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(54) **METHODS OF PREDICTING AND DECREASING THE RISK OF PREGNANCY LOSS**

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(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Described are methods for diagnosing and predicting the risk of pregnancy loss in a subject based on the presence of an aberrant humoral response to three proteins, Apolipoprotein B-100, alpha2macroglobulin (alpha2M), and fibronectin. The presence or a detectable level of maternal IgG antibodies to trophoblast-derived fibronectin and/or ApoB-100, and/or the absence or a non-detectable level of antibodies specifically binding to alpha2M is associated with a history of RPL and an increased risk of pregnancy loss. Also described are methods for identifying subjects at risk of pregnancy loss, selecting subjects for participation in a clinical study, and methods of decreasing the risk of pregnancy loss in a subject which include detecting the presence or absence of antibodies to one or more of trophoblast-derived ApoB-100, alpha2M, and fibronectin. Also provided are kits that contain ApoB-100, alpha2M, and fibronectin.

17 Claims, 7 Drawing Sheets

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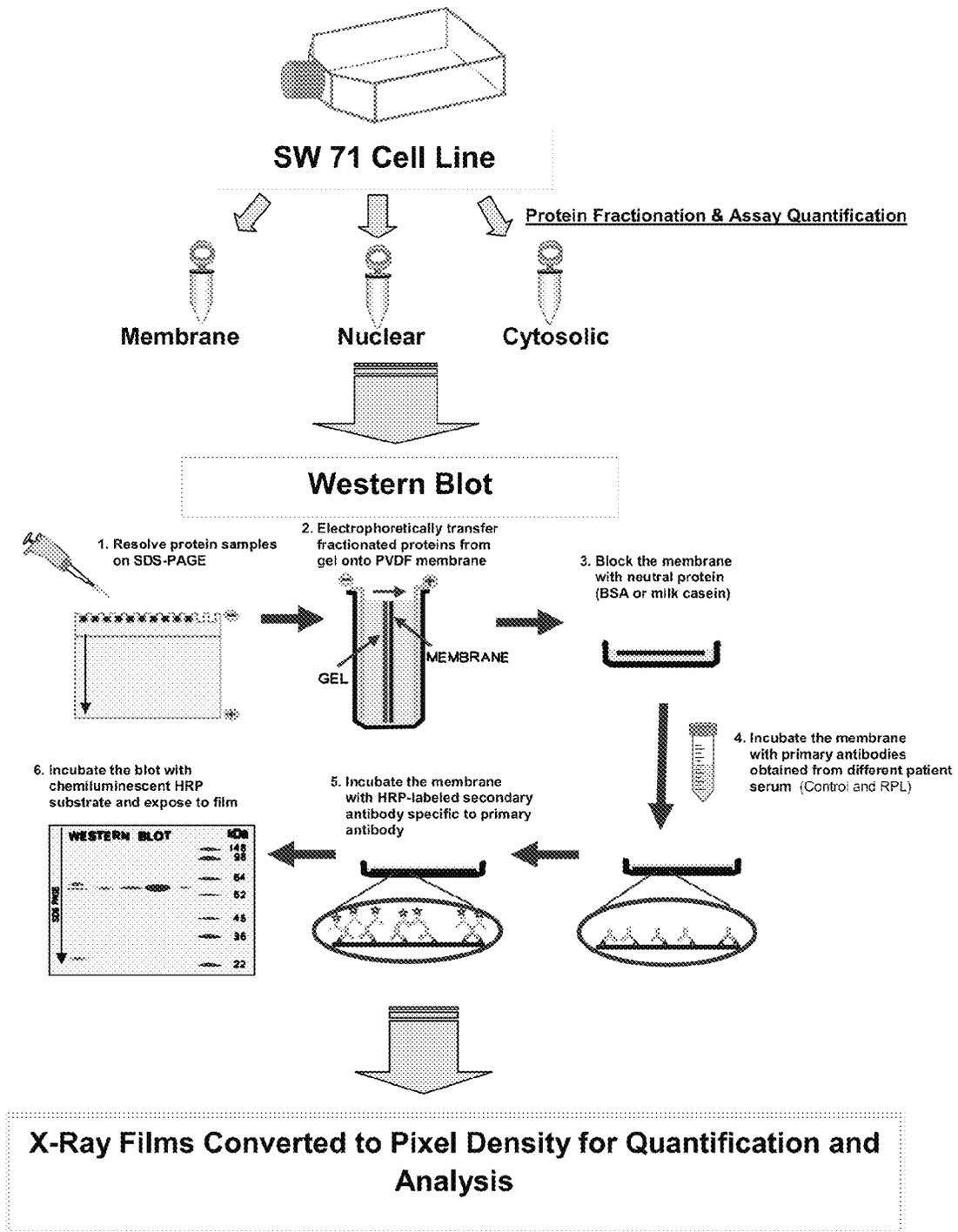
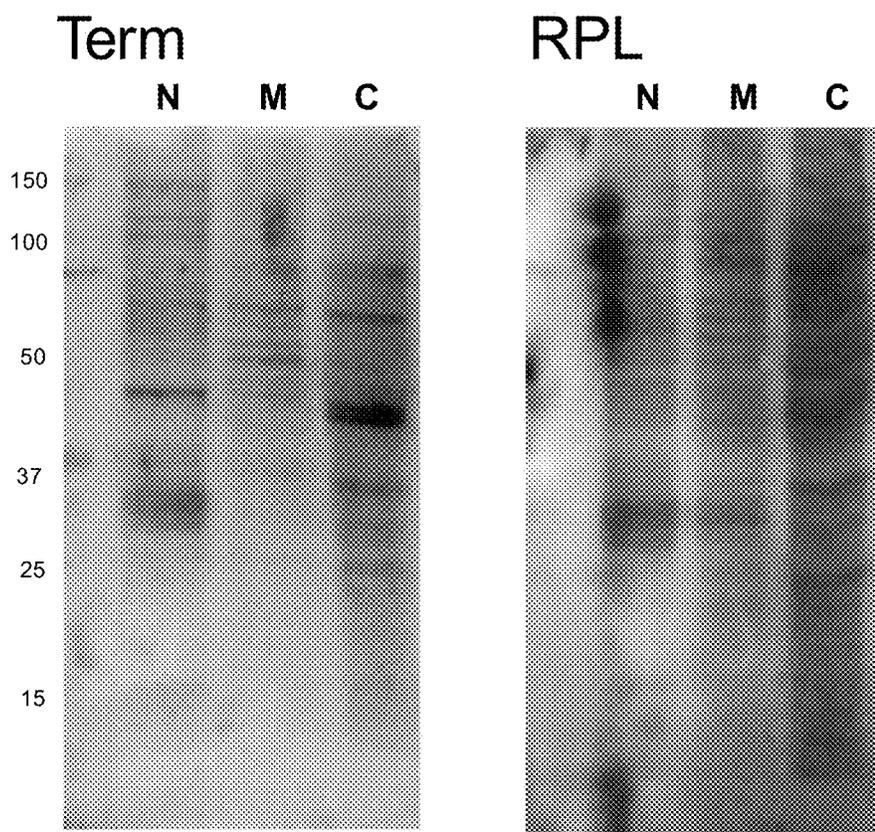


Figure 1



	RPL Immunoreactivity	P value
Nuclear	3.6 fold greater	p = 0.0044
Membrane	4.1 fold greater	P = 0.0001
Cytosol	1.8 fold greater	P = 0.0113

Figure 2

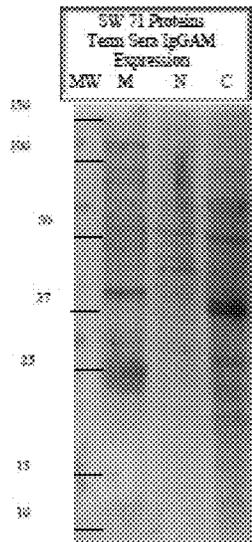


Figure 3A

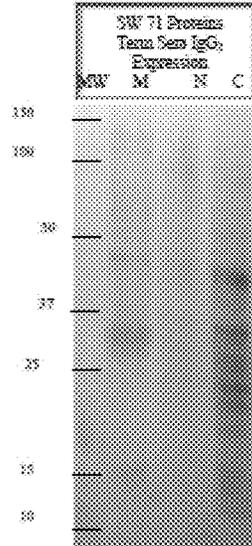


Figure 3B

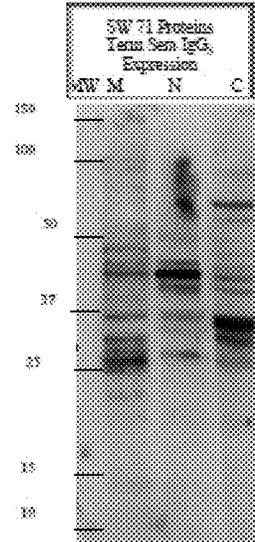


Figure 3C

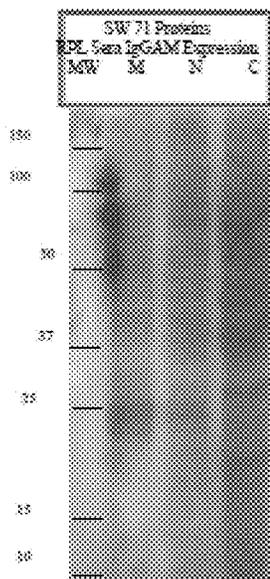


Figure 3D

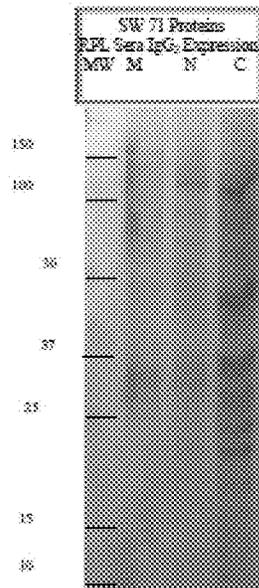


Figure 3E

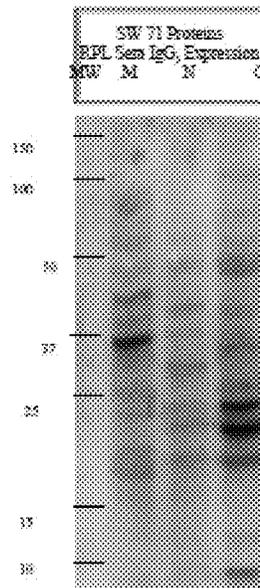


Figure 3F

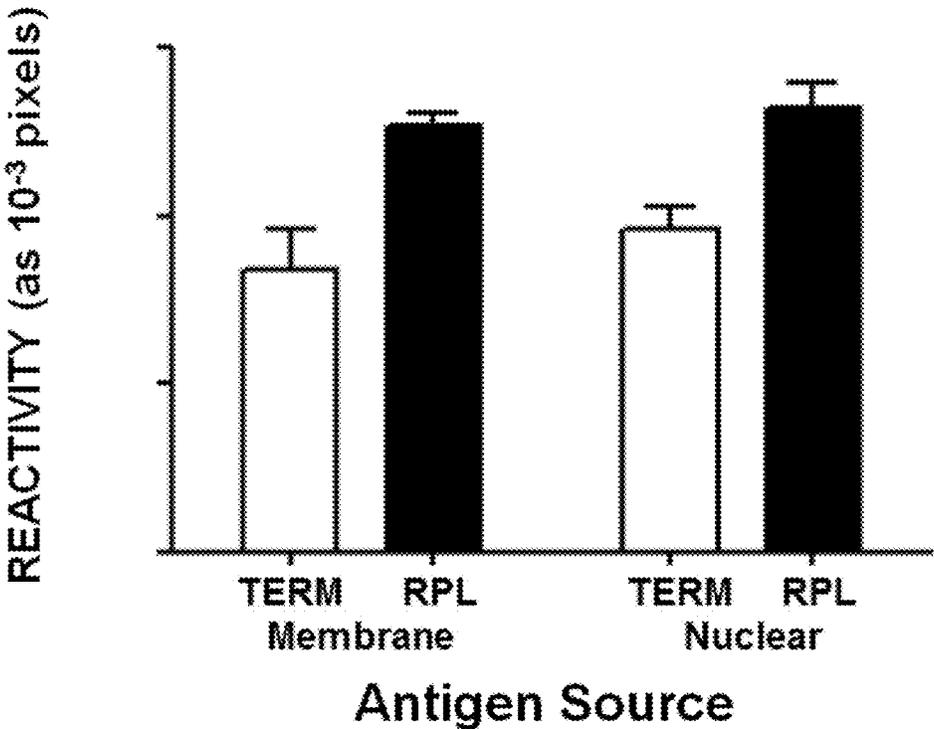


Figure 4

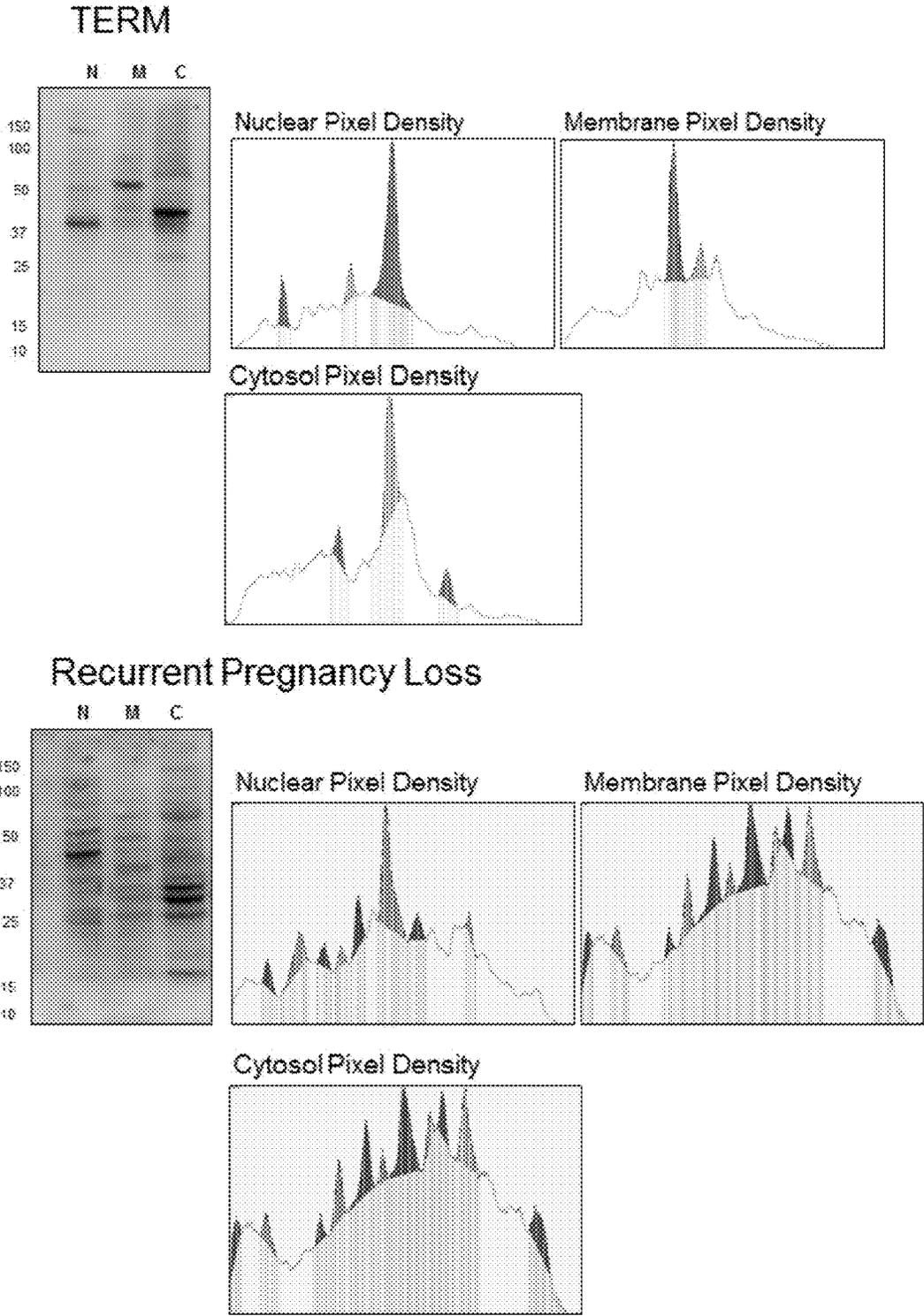


Figure 5

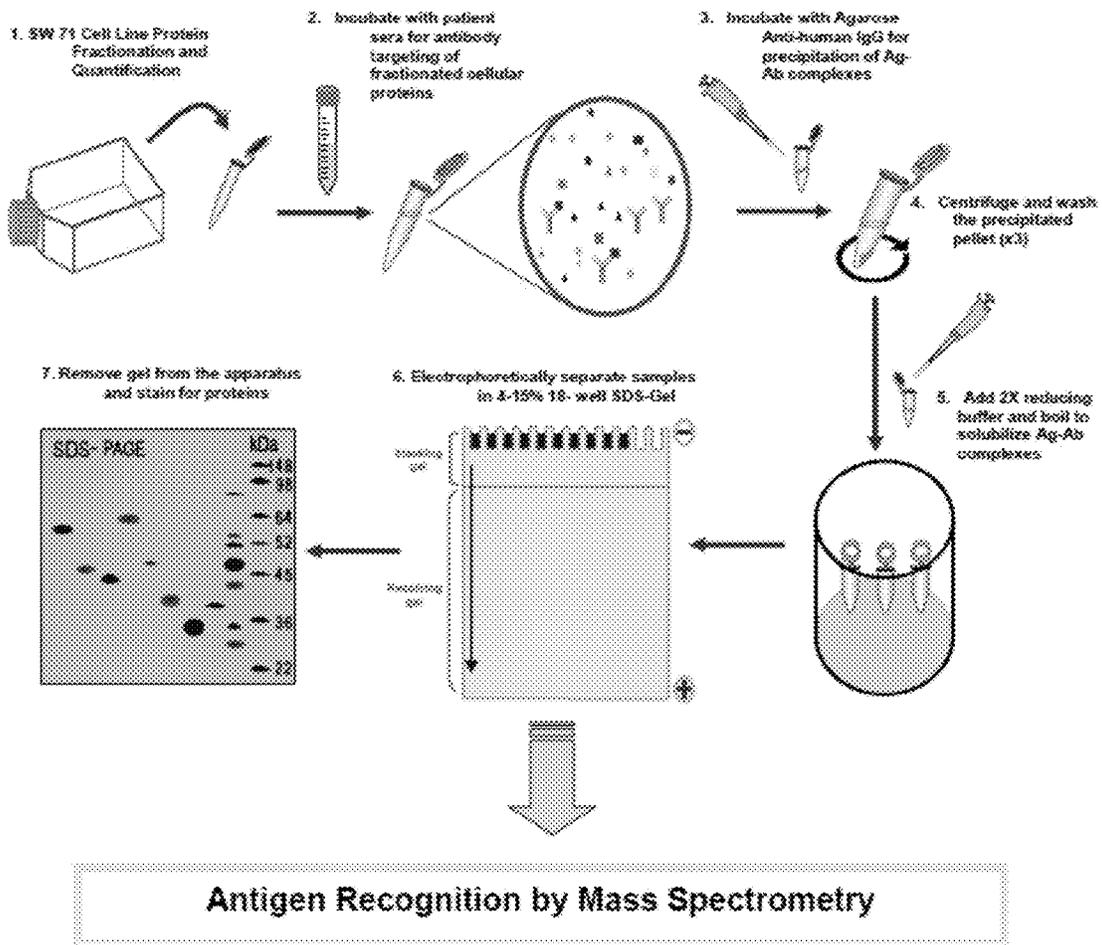


Figure 6

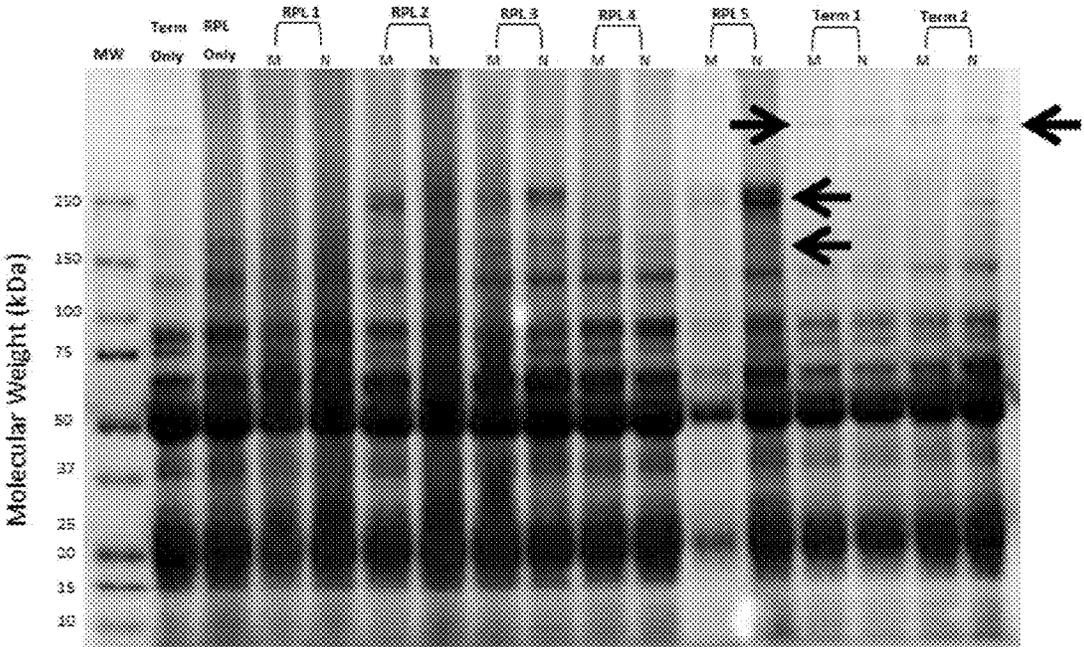


Figure 7

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METHODS OF PREDICTING AND DECREASING THE RISK OF PREGNANCY LOSS

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 13/583,981, filed on Sep. 11, 2012, which is a U.S. National Phase Application of International Patent Application No. PCT/US2011/028192, filed Mar. 11, 2011, entitled "METHODS OF PREDICTING AND DECREASING THE RISK OF PREGNANCY LOSS," which claims priority to U.S. Application No. 61/313,024, filed on Mar. 11, 2010, the entire contents of each of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD

This invention relates to biomarkers of recurrent pregnancy loss, and methods of use thereof.

BACKGROUND

Miscarriage occurs in an estimated 10% to 15% of all pregnancies of less than 20 weeks gestation (Stirrat, *Lancet* 336:673-675, 1990). Recurrent miscarriage is classically defined as the occurrence of three or more consecutive losses of clinically-recognized pregnancies prior to the 20th week of gestation, exclusive of molar and ectopic pregnancies. Prospective studies have assessed the risks of subsequent miscarriage after one miscarriage to be 15%, rising to 17% to 31% after two miscarriages, and 25% to 46% after three or more miscarriages. Although the loss of one pregnancy (or sometimes even two pregnancies) is considered by many clinicians to be within the range of normal (and likely due to gamete failure), loss of three or more pregnancies is generally considered to be associated with a pathological condition. Most providers will initiate an evaluation for recurrent pregnancy loss (RPL) after two or more consecutive miscarriages.

SUMMARY

The present invention is based, at least in part, on the discovery and characterization of differences in the humoral immune responses from women with a history of recurrent pregnancy loss (RPL) compared to multiparous women with an uncomplicated obstetrical history in terms of IgG subclasses and trophoblast cell antigens recognized. Thus, the present invention includes methods for diagnosing and predicting the risk of pregnancy loss based on the presence of an aberrant humoral response, specifically to three proteins, Apolipoprotein B-100 (ApoB-100), alpha2macroglobulin (α 2M), and fibronectin. The presence, a detectable level, or an increase of maternal IgG antibodies to trophoblast-derived fibronectin and/or Apolipoprotein B-100, and/or the presence, a detectable level, or a increase of antibody recognition to α 2M is associated with a history of RPL and an increased risk of future pregnancy loss.

Provided are methods of predicting the risk of pregnancy loss in a subject (i.e., a female subject) including providing a sample containing serum from the subject; and detecting the presence, absence, or levels of antibodies to one or more (e.g., one, two, or three) of fibronectin (protein or nucleic acid), α 2M (protein or nucleic acid), and ApoB-100 (protein or nucleic acid) in the sample, wherein the presence or a detectable level of antibodies to fibronectin (protein or nucleic acid)

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and/or ApoB-100 (protein or nucleic acid), and/or the presence or a detectable level of antibodies to α 2M (protein or nucleic acid) in the sample indicates that the subject has an increased risk of pregnancy loss. Some embodiments of these methods include providing a sample containing serum from the subject, detecting the presence or absence of antibodies to fibronectin in the sample, wherein the presence of antibodies to fibronectin in the sample indicates that the subject has an increased risk of pregnancy loss. Some embodiments of these methods further include detecting the presence or absence of antibodies to ApoB-100 in the sample, wherein the presence of antibodies to fibronectin to ApoB-100 indicates that the subject has an increased risk of pregnancy loss. Some embodiments of these methods further include detecting the absence or presence of antibodies to α 2M in the sample, wherein the presence of antibodies to fibronectin or ApoB-100, or the presence of antibodies to α 2M indicates that the subject has an increased risk of pregnancy loss.

Also provided are methods of identifying a subject at risk of pregnancy loss including providing a sample containing serum from the subject, and detecting the presence, absence, or level of antibodies to one or more (e.g., one, two, or three) of fibronectin (protein or nucleic acid), α 2M (protein or nucleic acid), and ApoB-100 (protein or nucleic acid) in the sample, wherein a subject having antibodies to fibronectin (protein or nucleic acid) and/or ApoB-100 (protein or nucleic acid), and/or having or having a detectable level of antibodies to α 2M (protein or nucleic acid) in the sample is identified as being at risk of pregnancy loss. Some embodiments of these methods include providing a sample containing serum from the subject, and detecting the presence or absence of antibodies to fibronectin in the sample, wherein a subject having antibodies to fibronectin present in the sample is identified as being at risk of pregnancy loss. Some embodiments of these methods further include detecting the presence or absence of antibodies to ApoB-100 in the sample, wherein a subject having antibodies to fibronectin or ApoB-100 present in the sample is identified as being at risk of pregnancy loss. Some embodiments of these methods further include detecting the presence or absence of antibodies to α 2M in the sample, wherein a subject having antibodies to fibronectin or ApoB-100, or having antibodies to α 2M present in the sample is identified as being at risk of pregnancy loss.

Also provided are methods of selecting a subject for participation in a clinical study including providing a sample containing serum from the sample, and detecting the presence or absence of antibodies to one or more (e.g., one, two, or three) of fibronectin (protein or nucleic acid), α 2M (protein or nucleic acid), and apolipoprotein B (protein or nucleic acid) in the sample, wherein a subject having antibodies to fibronectin (protein or nucleic acid) and/or ApoB-100 (protein or nucleic acid), and/or having or having a detectable level of antibodies to α 2M (protein or nucleic acid) in the sample is selected for participation in a clinical study. Some embodiments of these methods include providing a sample containing serum from the subject and detecting the presence or absence of antibodies to fibronectin in the sample, wherein a subject having antibodies to fibronectin present in the sample is selected for participation in a clinical study. Some embodiments of these methods further include detecting the presence or absence of antibodies to ApoB-100 in the sample, wherein a subject having antibodies to fibronectin or ApoB-100 present in the sample is selected for participation in a clinical study. Some embodiments of these methods further include detecting the presence or absence of antibodies to α 2M in the sample, wherein a subject having antibodies to fibronectin or ApoB-

100, or having antibodies to α 2M present in the sample is selected for participation in a clinical study.

Also provided are methods of decreasing the risk of pregnancy loss in a subject including providing a sample containing serum from the subject, detecting the presence or absence of antibodies to one or more (e.g., one, two, or three) of fibronectin (protein or nucleic acid), α 2M (protein or nucleic acid), and ApoB-100 (protein or nucleic acid) in the sample, and administering a therapeutic treatment to a subject having antibodies to fibronectin (protein or nucleic acid) and/or ApoB-100 (protein or nucleic acid), and/or having or having a detectable level of antibodies to α 2M (protein or mRNA) in the sample. Some embodiments of these methods include providing a sample comprising serum from the subject, detecting the presence or absence of antibodies to fibronectin in the sample, and administering a therapeutic treatment to a subject having antibodies to fibronectin present in the sample. Some embodiments of these methods further include detecting the presence or absence of antibodies to ApoB-100 in the sample, and administering a therapeutic treatment to a subject having antibodies to fibronectin or ApoB-100 present in the sample. Some embodiments of these methods further include detecting the presence or absence of antibodies to α 2M in the sample, and administering a therapeutic treatment to a subject having antibodies to fibronectin or ApoB-100, or having antibodies to α 2M present in the sample. In some embodiments of these methods, the therapeutic treatment is selected from complement inhibitors, hormone treatment, steroid treatment, passive immunotherapy with intravenous immunoglobulins, aspirin, and tumor necrosis factor- α (TNF- α) antagonists.

In any of the methods described herein, the subject is pregnant. In any of the embodiments of all the methods described herein, the sample is obtained from the pregnant subject within the first 20 weeks (e.g., within the first 19 weeks, 18 weeks, 17 weeks, 16 weeks, 15 weeks, 14 weeks, 13 weeks, 12 weeks, 11 weeks, 10 weeks, 9 weeks, 8 weeks, 7 weeks, 6 weeks, 5 weeks, 4 weeks, 3 weeks, 2 weeks, or 1 week), within the first 13 weeks, or within the first 12 weeks of pregnancy.

In some embodiments of all of the methods described herein, the subject has had at least one (e.g., two, three, four, or five) previous pregnancy loss or is suspected of having had at least one (e.g., two, three, four, or five) previous pregnancy loss. In some embodiments of all of the methods described herein, the subject is not pregnant, but is planning or considering a future pregnancy.

In some embodiments of all of the methods described herein, the subject having had at least one previous pregnancy loss or suspected of having had at least one previous pregnancy loss may be pregnant or may not be pregnant. In some embodiments of all of the methods described herein, the sample is obtained within the first 20 weeks (e.g., within the first 19 weeks, 18 weeks, 17 weeks, 16 weeks, 15 weeks, 14 weeks, 13 weeks, 12 weeks, 11 weeks, 10 weeks, 9 weeks, 8 weeks, 7 weeks, 6 weeks, 5 weeks, 4 weeks, 3 weeks, 2 weeks, or 1 week), the first 13 weeks, or within the first 12 weeks of pregnancy from the pregnant subject that has had at least one previous pregnancy loss or is suspected of having had at least one previous pregnancy loss.

In some embodiments of all of the methods described herein, the detecting of the presence, absence, or levels of antibodies includes contacting the sample with one or more (e.g., one, two, and three) antigens selected from the group consisting of ApoB-100 (protein or nucleic acid), fibronectin (protein or nucleic acid), and α 2M (protein or nucleic acid), or antigenic fragments thereof, and detecting the binding of

antibodies in the sample to the antigens. In some embodiments, the antigens are immobilized on a surface, e.g., in an array or on beads. In some embodiments of all of the methods described herein, the ApoB-100 (protein or nucleic acid), fibronectin (protein or nucleic acid), and/or α 2M (protein or nucleic acid) are trophoblast-derived. In some embodiments of all of the methods described herein, the subject is human.

Also provided are kits, containing essentially, one or more (e.g., one, two, or three) ApoB-100 (protein or nucleic acid), fibronectin (protein or nucleic acid), and α 2M (protein or nucleic acid), or antigenic fragments thereof.

As used herein, a "subject" is a vertebrate, including any member of the class mammalia, including humans, domestic and farm animals, and zoo, sports or pet animals, such as mouse, rabbit, pig, sheep, goat, cattle, and higher primates. In preferred embodiments, the subject is a human.

By the phrase "suspected of having had a previous pregnancy loss" is meant a subject who previously experienced one or more (e.g., one, two, three, or four) symptoms of a miscarriage (e.g., vaginal bleeding, pelvic cramps, abdominal pain, persistent lower back ache, and blood clots or grayish tissue passing from the vagina), but was not diagnosed as being pregnant (e.g., not diagnosed by a health care professional or through the use of a home diagnostic kit) at the time these symptoms occurred.

By the phrase "a subject having had a previous pregnancy loss" is meant a subject that has previously had at least one (e.g., two, three, four, or five) miscarriage. For example, a subject may have been diagnosed as being pregnant by a health care professional (e.g., a physician, nurse, physician's assistant, or a laboratory technician) or through the use of a home diagnostic kit, and thereafter experienced one or more (e.g., two, three, four, or five) symptoms of a miscarriage (e.g., vaginal bleeding, pelvic cramps, abdominal pain, persistent lower back ache, and blood clots or grayish tissue passing from the vagina) or failed to carry the fetus to term. The one or more previous miscarriages may also be confirmed by a health care professional (e.g., a physician, a nurse, a physician's assistant, or a laboratory technician).

By the term "antigen" or "antigenic fragment" is meant any portion of a molecule (e.g., peptide, nucleic acid (e.g., mRNA), carbohydrate, or lipid, or any combination thereof) that is specifically recognized by an antibody. For example, an antigen or antigenic fragment may be a peptide containing at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids) contiguous amino acids. Exemplary peptide antigens or antigenic fragments contain at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids) contiguous amino acids of the sequence within any one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, and 18. The contiguous amino acid sequence may be present within any portion of the sequence of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, or 18, for example, a sequence starting at the N-terminus, a sequence ending at the C-terminus, or a sequence starting at any single amino acid within the sequence (with the exception of the last four amino acids at the C-terminus of the protein). Additional exemplary peptide antigens contain the sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, or 18.

Exemplary antigens or antigenic fragments that are nucleic acids contain at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides of the sequence within any one of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, and 17. The contiguous nucleotide sequence may be present within any portion of the sequence of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, or 17, for example, a sequence starting at the 5'-terminus, a sequence ending at the 3'-terminus, or a

sequence starting at any single nucleotide within the sequence (with the exception of the last four nucleotides at the 3'-terminus of the nucleic acid). Additional exemplary nucleic acid antigens contain the sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, or 17.

By the term "at risk of pregnancy loss" is meant a subject that has an increased risk of having a miscarriage during pregnancy as compared to a control population (e.g., a group of subjects of the same age, a group of subjects not diagnosed as having recurrent pregnancy loss, a group of subjects that have never have had a miscarriage, or a group of subjects that have never experienced, at a single time, a combination of three or more symptoms of a miscarriage).

By the phrase "a subject planning or considering future pregnancy" is meant a subject who is not pregnant, but is planning a future pregnancy or considering becoming pregnant in the future.

By the phrase "therapeutic treatment" is meant a treatment that may decrease (e.g., a significant decrease (as used herein, the term "decrease" is meant a statistically significant decrease), such as by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%) the risk of having a miscarriage in a subject. Non-limiting examples of the therapeutic treatment are known in the art and include, without limitation, complement inhibitors, hormone treatment, steroid treatment, passive immunotherapy with intravenous immunoglobulins, aspirin, and TNF- α antagonists. Examples of therapeutic treatments are described herein and additional examples of therapeutic treatments are known in the art.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic illustration of exemplary methods for obtaining trophoblast cellular proteins and performing Western blot analysis.

FIG. 2 is a representative Western immunoblot demonstrating the reactivity profile of total circulating antibody derived from control term-derived patients compared to RPL patients. First trimester SW-71 cell-line derived nuclear, cellular, and cytosolic proteins were applied to 10% SDS-PAGE gel, electrophoretically separated, and analyzed for subject autoantibody reactivity by Western immunoblotting utilizing sera derived from control and test (RPL) subjects. When comparing all RPL and Term Western blots, sera from women with a history of RPL exhibited greater immunoreactivities compared to controls, with a total antibody reactivity 3.6-fold greater with nuclear antigens ($p=0.0044$), a 4.1-fold greater reactivity with membrane-derived antigens ($p=0.0001$), and a 1.8-fold greater recognition of cytosolic antigens ($p=0.0113$).

FIGS. 3A-F are a set of six Western blots showing the results of experiments performed as diagramed in FIG. 1 in Term samples (3A-3C) and RPL samples (3D-3F), showing levels of IgGAM (3A and 3D), IgG2 (3B and 3E); and IgG3

(3C and 3F). MW, molecular weight; M, membrane protein fractions; N, nuclear protein fractions; and C, Cytosolic protein fractions.

FIG. 4 is a bar graph showing the reactivity of antibodies from control (Term) and RPL subjects to antigens derived from the membrane or nucleus of SW-71 cells. In these experiments, the Western blot x-ray films with antibody-antigen complexes were scanned, digitized, and then converted to pixel density. Immunoreactivities for antigens from nuclear, membrane, or cytosolic compartments were standardized and the mean values and standard deviations were calculated.

FIG. 5 is two Western blots and a set of six pixel density graphs correlated for each lane of Western blot antibody reactivity to trophoblast antigens: nuclear, membrane, and cytosolic. A representative Term Western blot and three related graphs for Term subjects are shown (top half) and a representative RPL Western blot and three correlated graphs for RPL subjects are depicted (bottom half). The RPL Western blot has 1.80-fold increased reactivity relative to the representative Term Western blot and its pixel density graphs.

FIG. 6 is a schematic illustration of exemplary methods for protein expression profiling with immunoprecipitation.

FIG. 7 depicts the incongruent antigen antibody complexes between the control (Term) and RPL subjects. The arrows indicate α 2-macroglobulin, fibronectin, and Apolipoprotein B-100.

DETAILED DESCRIPTION

While survival of the fetal allograft in the maternal allo-reactive environment remains unexplained, suppression of cellular immunity appears to be one manifestation of pregnancy that may be a critical factor in its success. The pathophysiology of recurrent pregnancy loss (RPL) is complex with many unknown contributing factors and mechanisms. Suggested causes currently applicable to clinical evaluation include anatomical uterine or pelvic defects, genetic, or molecular abnormalities, endocrine disorders, thrombophilias and anti-phospholipid antibody syndrome. However, in up to 50% of cases, no etiology can be identified (Szekeres-Bartho et al., *Hum. Reprod. Update* 14:27-35, 2008). Increasing evidence supports the involvement of various aberrant maternal-fetal immunoregulatory mechanisms and, while survival of the fetal allograft in the maternal allo-reactive environment remains unexplained, suppression of cellular immunity appears to be one manifestation of pregnancy that may be a critical factor in its success. The etiology of pregnancy loss varies and is often controversial, with multiple factors potentially involved, including genetic, anatomic, infectious, environmental, immunologic, endocrine, and hematologic causes.

Several pathways have been postulated regarding the normal pregnancy suppression of maternal immune responses, including the presence of asymmetric, protective antibodies, the induction of suppressor cells, the lack of specific classic major histocompatibility (MHC) antigens, production and release of suppression factors, Fas ligand (FasL)-mediated induction of T-cell apoptosis, and alteration in the T-helper 2 type (Th2) to T-helper 1 type (Th1) ratio (Choudhury et al., *Hum. Reprod. Update* 7:113-134, 2001; Giacomini et al., *Hum. Immunol.* 39:281-289, 1994; Gill et al., *Am. J. Reprod. Immunol.* 41:23-33, 1999; Guller et al., *Semin. Reprod. Endocrinol.* 17:39-44, 1999; Mellor et al., *Ann. Rev. Immunol.* 18:367-391, 2000; Zavazava et al., *Mol. Med. Today* 4:116-121, 1998; Jenkins et al., *Fertil. Steril.* 73:1206-1208, 2000; Wilson et al., *Fertil. Steril.* 76:915-917, 2001). The failure to

effectively modulate these complex and likely intertwined maternal immune responses can lead to failure of placentation. Some studies, for example, have suggested that the binding of altered auto-antibodies to the endometrium may impair embryo implantation. Aberrant implantation and subsequent placentation may play a critical role in the pathogenesis of partial or total rejection of the fetal allograft, leading to complications, such as spontaneous miscarriage.

Successful pregnancy is linked with a shift to a Th2 immune response (e.g., an elevated Th2/Th1 immune response ratio), characterized by an increased rate of antibody production (e.g., the production of fetal reactive IgG antibodies) and decreased cell-mediated responses. The theory of immunodystrophism has been proposed to account for the dichotomous Th1- and Th2-cytokine profile associated with human pregnancy loss and success, respectively. Endometrial lymphocytes of recurrent spontaneous aborters express distinct immune-phenotypic profiles that antedate implantation and suggest that endometrial immunologic conditions are intrinsically altered in recurrent aborters.

Activation of T-lymphocytes during pregnancy can result in one of two different cytokine profiles: Th2-secreted cytokines (e.g., IL-4, IL-5, and IL-10) that suppress cellular immunity and Th1-secreted cytokines (e.g., IFN- γ , IL-2, and TNF- α) that induce cellular immunity (e.g., T-cell activation). Failure to suppress T-cell activation may allow the generation of cellular fetal-reactive immune responses, a potential key causative factor in infertility and adverse pregnancy outcomes. An increase in the ratio of Th2 cytokines to Th1 cytokines is associated with successful pregnancy and a decrease in this ratio is associated with recurrent pregnancy loss (Jenkins et al., *Fertil. Steril.* 73:1206-1208, 2000; Hill et al., *JAMA* 273:1933-1936, 1995). Clinical studies have demonstrated the predominance of Th1-type cytokine production in patients with pregnancy complications, such as pre-eclampsia (Hill et al., *JAMA* 273:1933-1936, 1995). There is no conclusive evidence as to whether some or all of these mechanisms are functional; however, it appears that mechanisms crucial for immunosuppression would be pivotal in early pregnancy.

A failure to suppress T-cell activation may allow the generation of cellular fetal-reactive immune responses, which may represent a key causative factor in infertility and adverse pregnancy outcomes. The data also indicate that the induction of IgG in normal pregnant patients is linked with a shift to a predominant IgG2 subclass, which does not appear to occur in women with recurrent pregnancy loss. One hypothesis is that, in women who suffer from recurrent pregnancy loss, the shift to anti-fetal immune responses lacking or exhibiting weak effector function fails to occur.

As demonstrated herein, women with a history of recurrent pregnancy loss demonstrate aberrant presence or absence of antibodies to three proteins: Apolipoprotein B-100, alpha2macroglobulin, and fibronectin. Thus, the presence, a detectable level, or an increase of maternal IgG antibodies to trophoblast-derived fibronectin (protein or nucleic acid) and/or ApoB-100 (protein or nucleic acid), and/or the presence, a detectable level, or a increase of antibodies that specifically bind to α 2M (protein or nucleic acid) is associated with a history of RPL and in increased risk of future pregnancy loss. Apolipoprotein B-100

Pregnancy is associated with a marked hyperlipidemia, mainly elevated plasma triglycerides and lipoproteins (Sarandol et al., *Clin. Biochem.* 37:990-996, 2004; Cekmen et al., *Clin. Biochem.* 36:575-578, 2003). Lipoproteins play a direct role on endothelial function and are highly susceptible to oxidation (Sarandol et al., *Arch. Gynecol. Obstet.* 270:157-

160, 2004). Apolipoprotein B (ApoB-100 and ApoB-48) provides a framework for packaging neutral lipids, such as triglycerides and cholesterol esters, into lipoproteins for transportation in circulation (Farese et al., *J. Lipid Res.* 37:347-360, 1996). Low density lipoprotein (LDL)-receptors mediate ApoB uptake into cells and protect against oxidation. Trophoblast cells express high levels of LDL-receptor and related proteins. Elevated serum levels of ApoB noted in intrauterine growth restriction (IUGR) fetuses suggest overproduction, lack of utilization, and/or aberrant intracellular uptake.

Lipoprotein oxidation has been proposed as a key player in the pathogenesis of pregnancy complications, such as pre-eclampsia and IUGR (Sarandol et al., *Arch. Gynecol. Obstet.* 270:157-160, 2004). In normal pregnancies, physiologic hyperlipidemia is believed to be controlled by anti-oxidative defense mechanisms, hormonal, or other biochemical influences (Cekmen et al., *Clin. Biochem.* 36:575-578, 2003; Sarandol et al., *Arch. Gynecol. Obstet.* 270:157-160, 2004). Aberrations in these control mechanisms may lead to lipid peroxidation products that mediate oxidative damage and result in disseminated endothelial dysfunction (Sarandol et al., *Clin. Biochem.* 37:990-996, 2004). Perhaps, in normal pregnancy, an enzyme or other substrate/protein/molecule stabilizes and/or utilizes lipoproteins, inhibiting the common pathway of oxidation.

Some researchers have proposed a role for antioxidants such as vitamin E and/or estrogen to inhibit oxidation of lipoproteins (Sarandol et al., *Arch. Gynecol. Obstet.* 270:157-160, 2004). Conversely, the absence of an endogenous protection mechanism may also lead to aberrant lipoprotein oxidative damage at the uteroplacental interface.

ApoB activity has been detected in the maternal corpus luteum during early pregnancy (Yamada et al., *Human Reprod.* 13:944-952, 1998). Corpus luteal cells produce and secrete abundant progesterone, synthesized from serum-derived cholesterol compounds. Studies show that ApoB represents uptake of LDL in to the luteal steroid producing cells. Human chorionic gonadotropin (HCG) administration enhanced levels of mRNA for the LDL receptor in luteal cells (Yamada et al., *Human Reprod.* 13:944-952, 1998; Benyo et al., *Endocrinology* 133:699-704, 1993). Endogenous or exogenous HCG may play a role in preserving and/or augmenting the presence of LDL-receptors, thereby maintaining the uptake of cholesterol compounds required for substantial progesterone production. Perhaps antibody recognition of ApoB in normal pregnant patients permits or supports its utilization in the luteal production and secretion of progesterone required in early pregnancy support and development. Conversely, perhaps patients who do not display this IgG recognition are subject to dysfunctional corpus luteum and subsequent recurrent pregnancy loss.

Expression of ApoB mRNA has been localized in the human embryo yolk endodermal cells (Cekmen et al., *Clin. Biochem.* 36:575-578, 2003). Detection of ApoB in the yolk sac of mice has lead to a probable model for transport and packaging of maternally-derived, nutrient rich ApoB-containing lipoproteins into the yolk sac of developing embryo (Cekmen et al., *Clin. Biochem.* 36:575-578, 2003). Perhaps, humoral recognition of ApoB in normal pregnancies plays a potential role in the nutrient support of the maturing embryo, and a lack of antibody recognition results in failure of continued embryo development.

The sequence of human Apolipoprotein B 100 can be found at NM_000384.2 (nucleic acid; SEQ ID NO: 1) and NP_000375.2 (protein; SEQ ID NO: 2).

Some embodiments of all of the methods described herein include the detection or determination of the presence, a detectable level, or an increase in the level of antibodies that specifically bind to apolipoprotein B-100 or an antigenic fragment thereof. The detected antibodies may be antibodies that specifically bind to an apolipoprotein B-100 protein, or an antigenic fragment thereof, or an apolipoprotein B-100 nucleic acid (e.g., mRNA), or an antigenic fragment thereof. For example, an antibody may specifically bind to at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids in the sequence of SEQ ID NO: 2. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 2 may be located anywhere within the sequence, for example, the contiguous amino acid sequence may begin at the N-terminus, may end at the C-terminus, or may begin at any amino acid within the sequence of SEQ ID NO: 2 (except for the last four C-terminal amino acids). In some embodiments, the detected antibody may specifically bind to polypeptide containing the sequence of SEQ ID NO: 2.

The detected antibodies may be antibodies that specifically bind to an apolipoprotein nucleic acid (e.g., mRNA) or an antigenic fragment thereof. For example, the detected antibody may specifically bind to at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides present within the sequence of SEQ ID NO: 1. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 1 may be located anywhere within the sequence, for example, the contiguous nucleotide sequence may begin at the 5'-terminus, may end at the 3'-terminus, or may begin at any nucleotide within the sequence of SEQ ID NO: 1 (except for the last four 3'-terminal nucleotides). In some embodiments, the detected antibody may specifically bind to a nucleic acid containing the sequence of SEQ ID NO: 1.

Additional embodiments of all of the methods described herein (e.g., methods for determining the risk of pregnancy loss in a subject, for identifying a subject at risk of pregnancy loss, for selecting a subject for participation in a clinical study, and for decreasing the risk of pregnancy loss in a subject) involve the detection or determination of the presence, a detectable level, or an increased level of Apolipoprotein B-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof, in a sample from the subject (e.g., in the serum of the subject). In these methods, the Apolipoprotein B-100 protein that is detected may be, for example, a protein containing the sequence of SEQ ID NO: 2, or any antigenic fragment thereof. For example, an antigenic fragment of Apolipoprotein B-100 protein that may be detected can contain at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 2. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 2 may be located anywhere within the sequence, for example, the contiguous amino acid sequence may begin at the N-terminus, may end at the C-terminus, or may begin at any amino acid within the sequence of SEQ ID NO: 2 (except for the last four C-terminal amino acids).

In additional examples of these methods, the Apolipoprotein nucleic acid (e.g., mRNA) that is detected may be, for example, a nucleic acid containing the sequence of SEQ ID NO: 1, or any antigenic fragment thereof. For example, an antigenic fragment of Apolipoprotein B-100 nucleic acid that may be detected can contain at least 5 (e.g., at least 6, 7, 8, 9,

10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 1. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 1 may be located anywhere within the sequence, for example, the contiguous nucleotide sequence may begin at the 5'-terminus, may end at the 3'-terminus, or may begin at any nucleotide within the sequence of SEQ ID NO: 1 (except for the last four 3'-terminal nucleotides).

Fibronectin

The maternal extracellular matrix and maternal-fetal interface have been suggested to play a pivotal role in conditions of early recurrent abortions, intrauterine growth restriction, and pre-eclampsia. Fetal fibronectin is one extracellular matrix protein that may act as "trophoblast glue," with increased concentrations at the chorionic-decidual margin and surrounding the extravillous trophoblasts (Mercorio et al., *Eur. J. Gynecol. Reprod. Biol.* 126:165-169, 2006; Guller et al., *Up-To-Date*, version 17.3, 2009). Integrin receptors for fibronectin with strong binding activity have been observed on the surface of blastocysts (Mercorio et al., *Eur. J. Gynecol. Reprod. Biol.* 126:165-169, 2006). Derangement in the signals and receptivity between cellular matrix proteins, e.g., fibronectin, and cell adhesion molecules may be responsible for pregnancy failure.

The fibronectin gene has three regions subject to alternative splicing, with the potential to produce 20 different transcript variants. The human reference sequences are as follows: NM_002026.2 (nucleic acid; SEQ ID NO: 3) and NP_002017.1 (protein; SEQ ID NO: 4) for fibronectin 1 isoform 3 preproprotein; NM_054034.2 (nucleic acid; SEQ ID NO: 5) and NP_473375.2 (protein; SEQ ID NO: 6) for fibronectin 1 isoform 7 preproprotein; NM_212474.1 (nucleic acid; SEQ ID NO: 7) and NP_997639.1 (protein; SEQ ID NO: 8) for fibronectin 1 isoform 6 preproprotein; NM_212475.1 (nucleic acid; SEQ ID NO: 9) and NP_997640.1 (protein; SEQ ID NO: 10) for fibronectin 1 isoform 2 preproprotein; NM_212476.1 (nucleic acid; SEQ ID NO: 11) and NP_997641.1 (protein; SEQ ID NO: 12) for fibronectin 1 isoform 5 preproprotein; NM_212478.1 (nucleic acid; SEQ ID NO: 13) and NP_997643.1 (protein; SEQ ID NO: 14) for fibronectin 1 isoform 4 preproprotein; and NM_212482.1 (nucleic acid; SEQ ID NO: 15) and NP_997647.1 (protein; SEQ ID NO: 16) for fibronectin 1 isoform 1 preproprotein (the longest transcript that encodes the longest isoform).

Some embodiments of all of the methods described herein include the determination of the presence, a detectable level, or an increase in the level of antibodies that specifically bind to fibronectin or an antigenic fragment thereof. The detected antibodies may be antibodies that specifically bind to a fibronectin protein or an antigenic fragment thereof, or a fibronectin nucleic acid (e.g., mRNA), or an antigenic fragment thereof. For example, an antibody may specifically bind to at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids in the sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, or 16. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NOS: 4, 6, 8, 10, 12, 14, or 16 may be located anywhere within the sequence, for example, the contiguous amino acid sequence may begin at the N-terminus, may end at the C-terminus, or may begin at any amino acid within the sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, or 16 (except for the last four C-terminal amino acids in any one of these sequences). In some

embodiments, the detected antibody may specifically bind to polypeptide containing the sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, or 16.

The detected antibodies may be antibodies that specifically bind to a fibronectin nucleic acid (e.g., mRNA). For example, the detected antibody may specifically bind to at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides present within the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15 may be located anywhere within the sequence, for example, the contiguous nucleotide sequence may begin at the 5'-terminus, may end at the 3'-terminus, or may begin at any nucleotide within the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15 (except for the last four 3'-terminal nucleotides of any one of these sequences). In some embodiments, the detected antibody may specifically bind to a nucleic acid containing the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15.

In additional embodiments of the methods described herein (e.g., methods for determining the risk of pregnancy loss in a subject, for identifying a subject at risk of pregnancy loss, for selecting a subject for participation in a clinical study, and for decreasing the risk of pregnancy loss in a subject) involve the detection of the presence, a detectable level, or an increased level of fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof, in a sample from the subject (e.g., in the serum of the subject). In these methods, the fibronectin protein that is detected may be, for example, a protein containing the sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, or 16, or any antigenic fragment thereof. For example, an antigenic fragment of a fibronectin protein that may be detected can contain at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, or 16. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, or 16 may be located anywhere within the sequence, for example, the contiguous amino acid sequence may begin at the N-terminus, may end at the C-terminus, or may begin at any amino acid within the sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, or 16 (except for the last four C-terminal amino acids of any one of the sequences).

In additional examples of these methods, the fibronectin nucleic acid (e.g., mRNA) that is detected may be, for example, a nucleic acid containing the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15, or any antigenic fragment thereof. For example, an antigenic fragment of a fibronectin nucleic acid that may be detected can contain at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15 may be located anywhere within the sequence, for example, the contiguous nucleotide sequence may begin at the 5'-terminus, may end at the 3'-terminus, or may begin at any nucleotide within the sequence of SEQ ID NO: 3, 5, 7, 9, 11, 13, or 15 (except for the last four 3'-terminal nucleotides). Alpha2-macroglobulin

Alpha2-macroglobulin (α 2M) is a major inhibitor of endoproteinases and carries a regulatory role in the protection, transport, and clearance of cytokines and growth factors (Esadeg et al., *Placenta* 24:912-921, 2003). α 2M has a potential means of immunosuppression in the human uteroplacental

interface and may be subject to transplacental transport to the neonate (Benyo et al., *Endocrinology* 133:699-704, 1993). α 2M targets cytokines to cells expressing the α 2M-receptor or lipoprotein-receptor related protein (Esadeg et al., *Placenta* 24:912-921, 2003; Shimizu et al., *Exp. Anim.* 51:361-365, 2002). Uterine α 2M is thought to originate from endothelial cells lining the endometrial vessels. Small serum concentrations of α 2M are found in normal healthy adults, and its concentration has been reported to double or triple during the secretory phase of the menstrual cycle suggesting a role as a decidualization protein (Esadeg et al., *Placenta* 24:912-921, 2003). During pregnancy, a receptor for the α 2M-proteinase complex has been demonstrated on the human placental syncytiotrophoblasts (Thomas et al., *Placenta* 11:413-430, 1990; Jensen et al., *Placenta* 9:463-477, 1988). In addition, synthesis and secretion of α 2M has also been detected in the visceral yolk sac of fetal rats. The sequence of human α 2M can be found at NM_000014.4 (nucleic acid; SEQ ID NO: 17) and NP_000005.2 (amino acid; SEQ ID NO: 18).

Some embodiments of the methods described herein include the determination or detection of the presence, a detectable level, or an increased level of antibodies that specifically bind to α 2M or an antigenic fragment thereof. The detected antibodies may be antibodies that specifically bind to an α 2M protein, or an antigenic fragment thereof, or an α 2M nucleic acid (e.g., mRNA), or an antigenic fragment thereof. For example, an antibody may specifically bind to at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids in the sequence of SEQ ID NO: 18. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 18 may be located anywhere within the sequence, for example, the contiguous amino acid sequence may begin at the N-terminus, may end at the C-terminus, or may begin at any amino acid within the sequence of SEQ ID NO: 18 (except for the last four C-terminal amino acids). In some embodiments, the detected antibody may specifically bind to polypeptide containing the sequence of SEQ ID NO: 18.

The detected antibodies may be antibodies that specifically bind to an α 2M nucleic acid (e.g., mRNA). For example, the detected antibody may specifically bind to at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides present within the sequence of SEQ ID NO: 17. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 17 may be located anywhere within the sequence, for example, the contiguous nucleotide sequence may begin at the 5'-terminus, may end at the 3'-terminus, or may begin at any nucleotide within the sequence of SEQ ID NO: 17 (except for the last four 3'-terminal nucleotides). In some embodiments, the detected antibody may specifically bind to a nucleic acid containing the sequence of SEQ ID NO: 17.

In additional embodiments of all of the methods described herein (e.g., methods for determining the risk of pregnancy loss in a subject, for identifying a subject at risk of pregnancy loss, for selecting a subject for participation in a clinical study, and for decreasing the risk of pregnancy loss in a subject) involve the detection of the presence, a detectable level, or an increased level of α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof, in a sample from the subject (e.g., in the serum of the subject). In these methods, the α 2M protein that is detected may be, for example, a protein containing the sequence of SEQ ID NO: 18, or any antigenic fragment thereof. For example, an antigenic frag-

ment of α 2M protein that may be detected can contain at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 18. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous amino acids within the sequence of SEQ ID NO: 18 may be located anywhere within the sequence, for example, the contiguous amino acid sequence may begin at the N-terminus, may end at the C-terminus, or may begin at any amino acid within the sequence of SEQ ID NO: 18 (except for the last four C-terminal amino acids).

In additional examples of these methods, the α 2M nucleic acid (e.g., mRNA) that is detected may be, for example, a nucleic acid containing the sequence of SEQ ID NO: 17, or any antigenic fragment thereof. For example, an antigenic fragment of an α 2M nucleic acid that may be detected can contain at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 17. The at least 5 (e.g., at least 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) contiguous nucleotides within the sequence of SEQ ID NO: 17 may be located anywhere within the sequence, for example, the contiguous nucleotide sequence may begin at the 5'-terminus, may end at the 3'-terminus, or may begin at any nucleotide within the sequence of SEQ ID NO: 17 (except for the last four 3'-terminal nucleotides).

Methods of Predicting Pregnancy Loss

Provided herein are methods of predicting the risk of pregnancy loss in a subject that include providing a sample containing serum from the subject and detecting the presence, absence, or level of antibodies that specifically bind to one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, in the sample, wherein the presence, a detectable level, or an increased level of antibodies to a fibronectin (protein or nucleic acid) and/or ApoB-100 (protein or nucleic acid), or antigenic fragment thereof, and/or the presence, a detectable level, or an increased level of antibodies to an α 2M (protein or nucleic acid), or an antigenic fragment thereof, in the sample, indicate that the subject has an increased (e.g., a statistically significant increase, such as an increase of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) risk of pregnancy loss. Additional methods for predicting the risk of pregnancy loss in a subject may include providing a sample (e.g., a sample containing serum) from the subject and detecting the presence, absence, or level of one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, in the sample, wherein the presence, a detectable level, or an increased level of a fibronectin (protein or nucleic acid) and/or an ApoB-100 (protein or nucleic acid), or antigenic fragment thereof, and/or the presence, a detectable level, or an increased level of an α 2M (protein or nucleic acid), or antigenic fragment thereof, in the sample, indicate that the subject has an increased (e.g., a statistically significant increase, such as an increase of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) risk of pregnancy loss.

In some embodiments of all of the methods described herein, the subject may be a pregnant woman in the first (weeks 0-12) or second (weeks 13-27) trimester of pregnancy (e.g., any time between 0 to 20 weeks, 6 to 20 weeks, 6 to 12 weeks, or 24 weeks after conception). In some embodiments

of all of the methods described herein, the subject may be a pregnant subject within the first 20 weeks of pregnancy (e.g., within 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, or 19 weeks of pregnancy). Early pregnancy loss is defined as the termination of pregnancy before 20 weeks gestation or with a fetal weight of <500 g.

The subject (e.g., a pregnant subject or a non-pregnant subject) may also have had at least one (e.g., two, three, four, five, or six) pregnancy loss or may be suspected of having had at least one (e.g., two, three, four, five, or six) previous pregnancy loss. In some embodiments, the subject is within the first 20 weeks of pregnancy (e.g., within 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, or 19 weeks of pregnancy) and has had at least one (e.g., two, three, four, five, or six) pregnancy loss or is suspected of having had at least one (e.g., two, three, four, five, or six) pregnancy loss.

A sample (e.g., serum) from the subject may be collected from the subject prior to pregnancy, following a miscarriage or a suspected miscarriage, or at any time during pregnancy (e.g., within 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, or 20 weeks). Samples may be frozen or stored for a period of time (e.g., at least one day, two days, three days, four days, five days, six days, or 1 week) prior to detecting/determining the presence, absence, or level of antibodies to one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an Apolipoprotein B-100 (protein or nucleic acid), and an α 2M (protein or nucleic acid), and/or the presence, absence, or level of one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an Apolipoprotein B-100 (protein or nucleic acid), and an α 2M (protein or nucleic acid), or an antigenic portion thereof.

Any method known in the art can be used for detecting the presence of antibodies in a sample (e.g., antibodies that specifically bind to fibronectin (protein or mRNA), Apolipoprotein B-100 (protein or mRNA), or α 2M (protein or mRNA), or an antigenic portion thereof). For example, a sample from a subject (e.g., a sample containing serum, such as, serum, plasma, or blood), from a subject (e.g., any of the subjects described herein, such as a pregnant subject) can be contacted with all or an antigenic fragment of a protein or nucleic acid described herein (e.g., a fibronectin protein or nucleic acid, an α 2M protein or nucleic acid, and/or an ApoB-100 protein or nucleic acid, or an antigenic fragment thereof), and binding of any antibodies in the sample to these antigen(s) can be detected using methods known in the art.

For example, an array (e.g., any array, microarray, biochip, or point-of-care test as is known in the art) can be provided that comprises one or more of the proteins, nucleic acids, or antigenic fragments thereof, and the array can be contacted with the sample containing serum from the subject, and the binding of any antibodies present in the sample can be detected.

Methods for detecting binding of the antibodies are known in the art, and can include the use of secondary antibodies; alternatively, any other antibody-specific ligand can be used. The secondary antibodies are generally modified to be detectable, e.g., labeled. The term "labeled" is intended to encompass direct labeling by coupling (i.e., physically linking) a detectable substance to the secondary antibody, as well as indirect labeling of the multimeric antigen by reactivity with a detectable substance. Examples of detectable substances

include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase (HRP), alkaline phosphatase, β -galactosidase, and acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, and quantum dots, dichlorotriazinylamine fluorescein, dansyl chloride, and phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include green fluorescent protein and variants thereof, luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S , or ^3H . Methods for producing such labeled antibodies are known in the art, and many are commercially available.

In some embodiments, the methods further include determining the subtype of the antibodies that bind to the antigens, e.g., detecting the presence of IgG3 antibodies, which as described herein are associated with an increased humoral response and increased risk of pregnancy loss. Antibodies that bind to the Fc region of IgG3 are commercially available and may be used to determine the presence, level, or absence of IgG3 antibodies in the sample.

Any method of detecting the antibodies can be used, including but not limited to radioimmunoassays (RIA), enzyme-linked immunosorbent assays (ELISA), Western blotting, surface plasmon resonance, microfluidic devices, protein array, mass spectrometry, or other assays as known in the art. In some embodiments, the antigens can be produced in tetrameric form as described in US-2009-005425-A1.

As described herein, the invention provides methods for predicting pregnancy loss by detecting the presence of aberrant humoral response; as noted above, these methods can include the use of an array. The invention provides an array (i.e., "biochip" or "microarray") that includes immobilized antigens that facilitate the detection of a particular antibody or antibodies in a biological sample. Antigens that identify the antibodies as described herein can be included in a custom array for detecting subjects predisposed to pregnancy loss, e.g., RPL. For example, a custom array can include antigens that specifically bind antibodies to one or more (e.g., one, two, or three) of a fibronectin, an $\alpha 2\text{M}$, and an ApoB-100. The antigens can be a full-length protein, a full-length nucleic acid (e.g., an mRNA), or a fragment thereof (as described herein). The array can also include biomolecules that identify additional antibodies. The arrays can be used to develop a database of information using data obtained using the methods described herein.

The term "array," as used herein, generally refers to a predetermined spatial arrangement of binding ligands, antigens, or spatial arrangements of binding ligands or antigens. Arrays according to the present invention that include antigens immobilized on a surface may also be referred to as "antigen arrays." Arrays according to the present invention that comprise surfaces activated, adapted, prepared, or modified to facilitate the binding of antigens to the surface may also be referred to as "binding arrays." Further, the term "array" may be used herein to refer to multiple arrays arranged on a surface, such as would be the case where a surface bore multiple copies of an array. Such surfaces bearing multiple arrays may also be referred to as "multiple arrays" or "repeating arrays." The use of the term "array" herein may encompass antigen arrays, binding arrays, multiple arrays, and any combination thereof; the appropriate meaning will be apparent from context. An array can include antigens that detect antibodies and other proteins altered in a

subject who is likely to experience pregnancy loss. The array can be contacted with one or more biological samples from a subject; the samples can include fluid or solid samples from any tissue of the body including excretory fluids such as urine.

5 Non-urine samples include, but are not limited to serum, plasma, amniotic fluid, and placental tissue.

An array of the invention comprises a substrate. By "substrate" or "solid support" or other grammatical equivalents, herein is meant any material appropriate for the attachment of antigens and is amenable to at least one detection method. As will be appreciated by those in the art, the number of possible substrates is very large. Possible substrates include, but are not limited to, glass and modified or functionalized glass, plastics (including acrylics, polystyrene, and copolymers of styrene and other materials, polypropylene, polyethylene, polybutylene, polyurethanes, TEFLON®, etc.), polysaccharides, nylon or nitrocellulose, resins, silica or silica-based materials including silicon and modified silicon, carbon, metals, inorganic glasses, plastics, ceramics, and a variety of other polymers. In addition, as is known the art, the substrate may be coated with any number of materials, including polymers, such as dextrans, acrylamides, gelatins, or agarose. Such coatings can facilitate the use of the array with a biological sample derived from urine or serum.

A planar array of the invention will generally contain addressable locations (e.g., "pads," "addresses," or "micro-locations") of antigens in an array format. The size of the array will depend on the composition and end use of the array. The arrays can contain 1, 2, or more different antigens; in some embodiments, different portions of the same protein are also included, to detect antibodies that bind to different epitopes on the protein. Generally, the array will comprise from two to as many as 100,000 or more antigens, depending on the end use of the array. A microarray of the invention will generally comprise at least one antigen that identifies or "captures" an antibody present in a biological sample. In some embodiments, the compositions of the invention may not be in an array format; that is, for some embodiments, compositions comprising a single antigen may be made as well. In addition, in some arrays, multiple substrates may be used, either of different or identical compositions. Thus, for example, large planar arrays may comprise a plurality of smaller substrates.

As an alternative to planar arrays, bead-based assays in combination with flow cytometry have been developed to perform multiparametric immunoassays. In bead-based assay systems the antigens can be immobilized on addressable microspheres. Each antigen for each individual immunoassay is coupled to a distinct type of microsphere (i.e., "micro-bead") and the immunoassay reaction takes place on the surface of the microspheres. Dyed microspheres with discrete fluorescence intensities are loaded separately with their appropriate biomolecules. The different bead sets carrying different capture probes can be pooled as necessary to generate custom bead arrays. Bead arrays are then incubated with the sample in a single reaction vessel to perform the immunoassay.

In some embodiments, product formation of the antibody with their immobilized antigens can be detected with a fluorescence-based reporter system. The antibodies can be labeled directly by a fluorogen or detected by a second fluorescently-labeled capture biomolecule. The signal intensities derived from captured antibodies are measured in a flow cytometer. The flow cytometer first identifies each microsphere by its individual color code. Second the amount of captured antibody on each individual bead is measured by the second color fluorescence specific for the bound target. This

allows multiplexed quantitation of multiple targets from a single sample within the same experiment. Sensitivity, reliability, and accuracy are comparable to standard microtiter ELISA procedures. With bead-based immunoassay systems antibodies can be simultaneously quantified from biological samples. An advantage of bead-based systems is the individual coupling of the antibody to distinct microspheres.

Thus, microbead array technology can be used to sort antibodies bound to specific antigens using a plurality of microbeads, each of which can carry about 100,000 identical molecules of a specific antigen on its surface. Once captured, the antibody can be handled as fluid, referred to herein as a "fluid microarray."

An array can encompass any means for detecting an antibody. For example, microarrays can be biochips that provide high-density immobilized arrays of antigens, where antibody binding is monitored indirectly (e.g., via fluorescence). In addition, an array can be of a format that involves the capture of antibodies by biochemical or intermolecular interaction, coupled with direct detection by mass spectrometry (MS).

Arrays and microarrays that can be used with the methods described herein can be made according to the methods described in U.S. Pat. Nos. 6,329,209; 6,365,418; 6,406,921; 6,475,808; and 6,475,809, which are incorporated herein in their entirety. New arrays, to detect specific selections or sets of biomarkers described herein can also be made using the methods described in these patents.

The antigens can be immobilized on the surface using methods and materials that minimize the denaturing of the antigens, that minimize alterations in the structure of the antigens, or that minimize interactions between the antigens and the surface on which they are immobilized.

Surfaces useful in the arrays may be of any desired shape (form) and size. Non-limiting examples of surfaces include chips, continuous surfaces, curved surfaces, flexible surfaces, films, plates, sheets, tubes, and the like. Surfaces preferably have areas ranging from approximately a square micron to approximately 500 cm². The area, length, and width of surfaces according to the present invention may be varied according to the requirements of the assay to be performed. Considerations may include, for example, ease of handling, limitations of the material(s) of which the surface is formed, requirements of detection systems, requirements of deposition systems (e.g., arrayers), and the like.

In certain embodiments, it is desirable to employ a physical means for separating groups or arrays of binding islands or immobilized antigens: such physical separation facilitates exposure of different groups or arrays to different solutions of interest. Therefore, in certain embodiments, arrays are situated within wells of 96, 384, 1536, or 3456 microwell plates. In such embodiments, the bottoms of the wells may serve as surfaces for the formation of arrays, or arrays may be formed on other surfaces and then placed into wells. In certain embodiments, such as where a surface without wells is used, binding islands may be formed or antigens may be immobilized on a surface and a gasket having holes spatially arranged so that they correspond to the islands or antigens may be placed on the surface. Such a gasket is preferably liquid-tight. A gasket may be placed on a surface at any time during the process of making the array and may be removed if separation of groups or arrays is no longer necessary.

The immobilized antigens can bind to antibodies present in a biological sample overlying the immobilized antigens. For example, an antibody present in a biological sample can contact an immobilized antigen and bind to it, thereby facilitating detection of the antibody.

Modifications or binding of antibodies to antigens in solution or immobilized on an array may be detected using detection techniques known in the art. Examples of such techniques include immunological techniques such as competitive binding assays and sandwich assays; fluorescence detection using instruments such as confocal scanners, confocal microscopes, or CCD-based systems, and techniques such as fluorescence, fluorescence polarization (FP), fluorescence resonant energy transfer (FRET), total internal reflection fluorescence (TIRF), fluorescence correlation spectroscopy (FCS); colorimetric/spectrometric techniques; surface plasmon resonance, by which changes in mass of materials adsorbed at surfaces may be measured; techniques using radioisotopes, including conventional radioisotope binding and scintillation proximity assays so (SPA); mass spectroscopy, such as matrix-assisted laser desorption/ionization mass spectroscopy (MALDI) and MALDI-time of flight (TOF) mass spectroscopy; ellipsometry, which is an optical method of measuring thickness of protein films; quartz crystal microbalance (QCM), a very sensitive method for measuring mass of materials adsorbing to surfaces; scanning probe microscopies, such as AFM and SEM; and techniques such as electrochemical, impedance, acoustic, microwave, and IR/Raman detection. See, e.g., Mere L, et al., "Miniaturized FRET assays and microfluidics: key components for ultra-high-throughput screening," *Drug Discovery Today* 4(8):363-369 (1999), and references cited therein; Lakowicz, J. R., *Principles of Fluorescence Spectroscopy*, 2nd Edition, Plenum Press, 1999.

Arrays as described herein can be included in kits. Such kits may also include, as non-limiting examples, one or more of reagents useful for preparing antigens for immobilization onto binding islands or areas of an array, reagents useful in preparing a sample, or reagents useful for detecting binding of antibodies in a sample to immobilized antigens, control samples that include known antibodies and instructions for use.

For example, kits provided by the invention may essentially include one or more (e.g., one, two, three, four, five, or six) of a fibronectin (protein and/or nucleic acid), an α 2M (protein and/or nucleic acid), and an Apolipoprotein B-100 (protein and/or nucleic acid), or antigenic fragments thereof. Kits may also contain one or more (e.g., one, two, three, four, five, or six) antibodies that specifically bind to a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof. For example, the one or more antigens or the one or more antibodies provided in the kits may be immobilized on a surface (e.g., in the form of a ELISA assay).

In some embodiments of all the methods described herein, the presence, absence, or levels of one or more (e.g., one, two, or three) of fibronectin protein or mRNA, Apolipoprotein B-100 protein or mRNA, and α 2M protein or mRNA, or an antigenic fragment thereof, present in a sample (e.g., a sample containing serum) from the subject is determined. A variety of examples of fibronectin protein and nucleic acid (e.g., mRNA), Apolipoprotein B-100 protein and nucleic acid (e.g., mRNA), and α 2M protein and nucleic acid (e.g., mRNA), and antigenic fragments thereof are described herein. Methods for measuring the presence, absence, or levels of an antigenic protein or peptide in a biological sample using antibodies are known in the art, including, for example, radioimmunoassays (RIA), enzyme-linked immunosorbent assays (ELISA), Western blotting, surface plasmon resonance, microfluidic devices, protein array, and mass spectrometry. Methods for measuring the presence, absence, or levels of a nucleic acid in

a biological sample are known in the art, for example, polymerase chain reaction (PCR)-based techniques (e.g., real-time quantitative PCR and gene array). Primers for use in the methods of measuring the presence, absence, or levels of a nucleic acid may be designed based on the sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, or 17 using methods known in the art.

In any of the methods described herein, one or more (e.g., one, two, three, four, five, six, seven, or eight) of any combination of the following, in a sample from the subject, indicate that the subject has an increased (e.g., a statistically significant increase, such as an increase of 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) risk of pregnancy loss: the or a detectable level of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); a increase in the level of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age or a control subject that has had one or more successful pregnancies, or a subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); a decreased increased level of α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increase in the level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or detectable level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increased level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to an Apolipoprotein B-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); and an increase in the levels of antibodies that specifically bind to an Apolipoprotein B-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of an Apolipoprotein B-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); and an increased level of an Apolipoprotein B-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscar-

riage or is not suspected of having had a miscarriage). In any of methods described herein, the term “decrease” is meant a statistically significant decrease (e.g., by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%). In any of the methods described herein, the term “increase” is meant a statistically significant increase (e.g., by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%). By the term “non-detectable level” is meant a level of a protein, nucleic acid, or antibody that cannot be detected by the method used to perform the measurement in a given experiment. The non-detectable level of a protein, nucleic acid, or antibody will vary depending on the particular assay used to perform the measurement. By the term “detectable level” is meant a level of a protein, nucleic, or antibody that may be detected by the method used to perform the measurement in a given experiment.

20 Methods of Identifying a Subject at Risk of Pregnancy Loss

Also provided are methods of identifying a subject at risk (e.g., having an increased risk or pregnancy loss relative to a control population) of pregnancy loss that include providing a sample (e.g., a sample containing serum) from the subject and detecting the presence, absence, or level of antibodies that specifically bind to one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100, or an antigenic fragment thereof, in the sample, wherein the presence, a detectable level, or an increased level of antibodies to a fibronectin (protein or nucleic acid) and/or an ApoB-100 (protein or nucleic acid), or an antigenic fragment thereof, and/or the presence, a detectable level, or a increased level of antibodies to an α 2M (protein or nucleic acid), or antigenic fragment thereof, in the sample, identifies the subject as having an increased (e.g., a statistically significant increase, such as an increase of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) risk of pregnancy loss. Additional methods for identifying a subject at risk of pregnancy loss may include providing a sample (e.g., a sample containing serum) from the subject and detecting the presence, absence, or level of one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, in the sample, wherein the presence, a detectable level, or an increased level of a fibronectin (protein or nucleic acid) and/or an ApoB-100 (protein or nucleic acid), or antigenic fragment thereof, and/or the presence, a detectable level, or a increased-level of an α 2M (protein or nucleic acid), or antigenic fragment thereof, in the sample, identifies the subject as having an increased risk of pregnancy loss.

These methods may be performed on any of the subjects described herein. The method may be also be performed at any of the time points described herein.

The presence, absence, or levels of antibodies that specifically bind to a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), or an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, may be determined using any of the methods described herein or those known in the art. The presence, absence, or levels of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), or a Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, may be determined using any of the methods described herein or those known in the art.

In any of the methods described herein, one or more (e.g., one, two, three, four, five, six, seven, or eight) of any combination of the following, in a sample from the subject, identify the subject as being at risk (e.g., having an increased risk) of pregnancy loss: the presence or a detectable level of antibodies that specifically bind to an ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increase in the level of antibodies that specifically bind to an ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increased level of ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increase in the level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increased level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); and an increase in the levels of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); and an increased level of an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage).

Methods of Selecting a Subject for Participation in a Clinical Study

Also provided are methods of selecting a subject for participation in a clinical study that include providing a sample (e.g., a sample containing serum) from the subject and detecting the presence, absence, or level of antibodies that specifically bind to one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or

nucleic acid), or an antigenic fragment thereof, in the sample, wherein the presence, a detectable level, or an increased level of one or more antibodies that specifically bind to a fibronectin (protein or nucleic acid) and/or an ApoB-100 (protein or nucleic acid), or an antigenic fragment thereof, and/or the presence, a detectable level, or an increased level of antibodies that specifically bind to an α 2M (protein or nucleic acid), or antigenic fragment thereof, in the sample, indicates that the subject should be selected for participation in a clinical study. Additional methods for selecting a subject for participation in a clinical study may include providing a sample (e.g., a sample containing serum) from the subject and detecting the presence, absence, or level of one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, in the sample, wherein the presence, a detectable level, or an increased level of a fibronectin (protein or nucleic acid) and/or an ApoB-100 (protein or nucleic acid), or antigenic fragment thereof, and/or the presence, a detectable level, or an increased level of an α 2M (protein or nucleic acid), or antigenic fragment thereof, in the sample indicates that the subject should be selected for participation in a clinical study.

These methods may be performed on any of the subjects described herein. The method may be also be performed at any of the time points described herein.

The presence, absence, or levels of antibodies that specifically bind to a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), or a Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, may be determined using any of the methods described herein or those known in the art. The presence, absence, or levels of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), or a Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, may be determined using any of the methods described herein or those known in the art.

In any of the methods described herein, one or more (e.g., one, two, three, four, five, six, seven, or eight) of any combination of the following, in a sample from the subject, indicate that the subject should be selected for participation in a clinical study: the presence or a detectable level of antibodies that specifically bind to an ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increase in the level of antibodies that specifically bind to an ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increased level of ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increase in the level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); and an increase in the levels of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage).

and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); an increased level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein); and a decrease increase in the levels of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein) (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage). Methods for Decreasing the Risk of Pregnancy Loss

Also provided are methods of decreasing the risk of pregnancy loss in a subject that include providing a sample (e.g., a sample containing serum) from the subject; determining the presence, absence, or level of antibodies that specifically bind to one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, in the sample; and administering to the subject a therapeutic treatment if subject has, has a detectable level, or has an increased level of antibodies that specifically bind to a fibronectin (protein or nucleic acid) and/or an ApoB-100 (protein or nucleic acid), or an antigenic fragment thereof, and/or have, has a detectable level, or a increased level of antibodies that specifically bind to an α 2M (protein or nucleic acid), or antigenic fragment thereof in the sample. Additional methods of decreasing the risk of pregnancy loss in a subject include providing a sample (e.g., a sample containing serum) from the subject; determining the presence, absence, or level of one or more (e.g., one, two, or three) of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), and an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, in the sample; and administering to the subject a therapeutic treatment if subject has, has a detectable level, or has an increased level of a fibronectin (protein or nucleic acid) and/or an ApoB-100 (protein or nucleic acid), or antigenic fragment thereof, and/or have, has a detectable level, or a decreased increased level of an α 2M (protein or nucleic acid), or antigenic fragment thereof in the sample.

These methods may be performed on any of the subjects described herein. The method may be also be performed at any of the time points described herein. The methods may be used to select a subject for administration of a treatment to reduce the risk of a pregnancy loss.

The presence, absence, or levels of antibodies that specifically bind to a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), or a Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, may be

determined using any of the methods described herein or those known in the art. The presence, absence, or levels of a fibronectin (protein or nucleic acid), an α 2M (protein or nucleic acid), or an Apolipoprotein B-100 (protein or nucleic acid), or an antigenic fragment thereof, may be determined using any of the methods described herein or those known in the art.

In any of the methods described herein, at least one therapeutic treatment should be administered to a subject having one or more (e.g., one, two, three, four, five, six, seven, or eight) of any combination of the following features: the presence or a detectable level of antibodies that specifically bind to an ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample; an increase in the level of antibodies that specifically bind to an ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample; an increased level of ApoB-100 protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample; an increase in the level of antibodies that specifically bind to a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample; an increased level of a fibronectin protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample; and a increase in the levels of antibodies that specifically bind to an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies, and/or a subject that has not had a miscarriage or is not suspected of having had a miscarriage); the presence or a detectable level of an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample; and a increased level of an α 2M protein or nucleic acid (e.g., mRNA), or an antigenic fragment thereof (as described herein), in the sample (e.g., as compared to a control subject of the same age, a control subject that has had one or more successful pregnancies,

and/or a control subject that has not had a miscarriage or is not suspected of having had a miscarriage).

The therapeutic treatment may be administered by a health care professional (e.g., a physician, a nurse, or a physician's assistant). The treatment may be administered in a patient's home or in a health care facility (e.g., a hospital or a clinic). In some embodiments, the therapeutic treatment is a treatment that decreases or suppresses an immune response, e.g., that decreases inflammation, or decreases a Th1-type immune response, and/or enhances a Th2-type immune response.

Non-limiting examples of therapeutic treatment include complement inhibitors (e.g., antibodies that bind to complement components, such as C1, C3, and C5 (e.g., 5G1.1SC and 5G1.1 (Alexion), eculizumab, and pex-elizumab); soluble complement receptor 1, C1-inhibitor (C1-Inh), C1 esterase inhibitor, C3 inhibitor (POT-4), C5 complement inhibitor (Alexion), compstatin, heparin, and the complement inhibitors described in U.S. Pat. Nos. 4,146,640; 4,007,270; 4,241,301; and 5,847,082; and U.S. Patent Application Publications Nos. 2007/0141573; 2009/0117098; and 2009/0214538), hormones (e.g., progesterone), steroids (e.g., prednisone), passive immunotherapy with intravenous immunoglobulin, aspirin (e.g., low-dose aspirin), and TNF antagonists (e.g., soluble fragments of TNF- α receptors (e.g., etanercept) and antibodies that specifically bind to TNF- α (e.g., adalimumab and infliximab), and small molecule inhibitors of TNF- α (e.g., pentoxifyllene)). One or more (e.g., two, three, four, or five) therapeutic treatments may be administered to the subject. In some methods, the subject may be pregnant (e.g., within the first 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, or 20 weeks of pregnancy) or may be planning on becoming pregnant in the future (e.g., the therapeutic treatment is administered at least one month, at least 3 weeks, at least 2 weeks, at least 1 week prior to conception).

The dosage (e.g., 0.1 to 100 mg, 0.1 mg to 80 mg, 0.1 mg to 70 mg, 0.1 to 60 mg, 0.1 mg to 50 mg, 1 mg to 40 mg, 1 mg to 30 mg, 1 mg to 20 mg, and 1 mg to 10 mg) and administration regime (e.g., once a day, twice a day, three times a day, four times a day, once a week, twice a week, three times a week, four times a week, once every two weeks, once a month, twice a month, three times a month, or four times a month) of the therapeutic treatment may be determined by a health care professional based on the physical condition of the subject (e.g., age, health, pregnant or non-pregnant, and other health conditions) and based on the dosing and administration schedules known in the art (for a general review of exemplary treatments, see, Tincani et al., *Clinic Rev. Allerg. Immunol.* 39:153-159, 2010; Stephenson et al., *Human Reproduction* 25:2203-2209, 2010; and Dukhovny et al., *Curr. Opin. Endocrinol. Diabetes Obes.* 16:451-458, 2009). For example, a subject identified for the administration of a therapeutic treatment using the provided methods, may be intravenously administered passive immunoglobulin one or more times (e.g., two, three, four, or five times) during and/or prior to pregnancy (as described herein). A physician may monitor the subject (e.g., using the methods to determine the risk of pregnancy loss described herein) to determine whether the dosage or the frequency of therapeutic treatment should be altered (e.g., increase in the dosage and/or frequency of administration of a therapeutic treatment for those subjects indicated as having an increased risk of pregnancy loss) during a given time frame (e.g., during the term of the pregnancy (e.g., anywhere from between conception to 9 months of pregnancy, between conception and up to 8 months of pregnancy, between conception and up to 7 months of pregnancy,

between conception up to 6 months of pregnancy, between conception up to 5 months of pregnancy, between conception up to 4 months of pregnancy, between conception up to 3 months of pregnancy, between conception and up to 2 months of pregnancy, between 3 and 20 weeks of pregnancy, between 5 and 20 weeks of pregnancy, or between 10 and 20 weeks of pregnancy), a period of time prior to conception (e.g., within 6 months of conception, within 5 months of conception, within 4 months of conception, within 3 months of conception, within 2 months of conception, within 1 month of conception, within 3 weeks of conception, within 2 weeks of conception, within 1 week of conception, or within 3 days of conception), or a period of time beginning prior to conception (e.g., within 6 months of conception, within 5 months of conception, within 4 months of conception, within 3 months of conception, within 2 months of conception, within 1 month of conception, within 3 weeks of conception, within 2 weeks of conception, within 1 week of conception, or within 3 days of conception) to the end of the term or a time point during the term of the pregnancy (e.g., anywhere from between conception to 9 months of pregnancy, between conception and up to 8 months of pregnancy, between conception up to 7 months of pregnancy, between conception up to 6 months of pregnancy, between conception up to 5 months of pregnancy, between conception up to 4 months of pregnancy, between conception up to 3 months of pregnancy, between conception and up to 2 months of pregnancy, between 3 and 20 weeks of pregnancy, between 5 and 20 weeks of pregnancy, or between 10 and 20 weeks of pregnancy).

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Example 1

Alterations in Immune Responses in Women with Recurrent Pregnancy Loss

Current literature supports the concept that failure to suppress maternal lymphoid activation pathways and aberrant auto-antibody production is associated with pregnancy complications, from infertility to spontaneous recurrent pregnancy loss (RPL). These experiments were designed to enhance understanding of the human immunologic responses and antigen recognition patterns that develop during the first trimester in women with a history of RPL compared to first-trimester, multi-parous women with an uncomplicated obstetrical history.

Western immunoblotting using human serum-derived antibodies from RPL and healthy subjects and trophoblast-derived antigens was used to characterize a distinct difference in the total IgG recognition profiles among healthy pregnant controls and RPL patients (see, schematic diagram of the experimental method in FIG. 1). These antigens were obtained from the first trimester trophoblast-derived cell line, SW.71 (Yale University, New Haven, Conn., USA), which was maintained in DMEM/F12 (Gibco Invitrogen) media supplemented with 2 mL L-glutamine, 10% fetal bovine serum, 1 mM sodium pyruvate, 0.1 mM non-essential amino acids, 100 units/mL penicillin-streptomycin at 37° C. and 5% CO₂ in 75-cm² tissue culture flasks. This cell line was isolated from a seven-week placenta immortalized by ectopic expression of the catalytic subunit of human telomerase.

Nuclear, cellular, and cytoplasmic proteins were extracted from the Sw.71 cell-line derived using a cell fraction kit (BioVision, Mountain View, Calif., USA) using the manufacturer's instructions. The protein concentrations of each fraction were determined using Bio-Rad DC protein quantification assay (Bio-Rad Laboratories, Hercules, Calif., USA).

To visualize subject autoantibody reactivity patterns, these extracted, solubilized nuclear, cytosolic, and cellular membrane proteins (40 µg/lane) were applied to 10% SDS-PAGE gels and electrophoretically separated by the method of Laemmli (*Nature* 227:680-685, 1970). The reactive proteins were analyzed by Western immunoblotting (Brown et al., *Int. J. Cancer* 55:678-684, 1993). Nitrocellulose membranes were probed overnight at 4° C. with patient serum (diluted 1:100) and then washed three times in Tris-buffered saline (TBS). Western blotting was completed using peroxidase-conjugated anti-human IgG2, IgG3, and whole IgG (AbD Sertotec, Raleigh, N.C.). Bound antibody-antigen complexes were visualized using enhanced chemiluminescence (Immun-Star, Bio-Rad, Hercules, Calif.). The resulting x-ray film was scanned as a 16-bit grayscale JPEG image. This grayscale image was digitized and converted into pixel density using Un-scan-it software (Silk Scientific Corp., Orem, Utah). On each gel image, the number of pixels for all visualized bands was quantitated using Un-Scan-It and the total number of pixels for all bands within each lane was calculated. This total number of pixels for all bands in specific lanes was determined and the mean (average) total pixels for the specific lane for patients within each population (controls versus RPL) were calculated for antigens derived from the nuclear and membrane fractions.

for one patient (subject #8), who was euthyroid while receiving replacement medication. All were Caucasian except for one (subject #6), who was Chinese. None patients with a history of RPL had anticardiolipin antibodies or lupus anticoagulant. Seven women had a normal uterine contour by evaluation with either hysterosalpingography or saline infusion sonohysterography. Seven women had either a normal serum progesterone level (10 ng/mL) or an in-phase luteal biopsy result.

The data from these experiments demonstrate a distinct difference in the total IgG recognition profiles among healthy pregnant controls and RPL patients (FIGS. 2 and 3A-F). The data in FIGS. 2 and 3A-3F, indicate that sera from women with a history of RPL exhibited greater immunoreactivities compared to controls, with a total antibody reactivity 3.6-fold greater with nuclear antigens ($p=0.0044$), a 4.1-fold greater reactivity with membrane-derived antigens ($p=0.0001$), and a 1.8-fold greater recognition of cytosolic antigens ($p=0.0113$). Among IgG subclasses, a notably enhanced recognition pattern was observed in IgG3, which revealed an increase of 1.8-fold greater immunoreactivity than controls. This increase was consistently noted across all three antigen sources (nuclear, membrane, and cytosolic antigens), with antigens ranging from 15 to 250 kDa.

Western blots of antibody-antigen complexes, resulting from the use of patient serum as the source of primary antibodies, were scanned, digitized, and converted to pixel density. The pixel densities for these two groups of patients were compared for total IgG reactivity for antigens derived from the membrane, nuclear, and cytoplasmic

TABLE 1

Subjects										
Subject	Age (yrs)	Gravidity	Parity	No of abortions	ACA	LAC	HSG/SIS	Karyotype	EB/P4	TSH
#1	32	3	0	3	X	X	X	F		X
#2	29	5	0	5	X	X				X
#3	26	3	0	3	X	X	X			
#4	36	3	0	3	X	X	X	F		X
#5	32	3	0	3	X	X			X	X
#6	35	5	0	5	X	X	X	F	X	
#7	25	3	0	3	X	X	X	M, F		X
#8	30	3	0	3	X	X		M	X	X

The serum samples used in the experiments described herein were obtained from first trimester pregnant women who either had had ≥ 2 recurrent spontaneous abortions without a successful pregnancy ($n=8$) or had had two or more term, uncomplicated deliveries ($n=2$). Patients with histories of RPL were in their first trimester of pregnancy with a history of two or more recurrent consecutive miscarriages of unknown etiology (i.e., with documented normal maternal and paternal karyotypes, normal uterine cavity imaging and/or assessment, and normal thrombophilia profile). Venous blood samples were obtained, allowed to clot, and sera isolated. These samples were obtained from volunteers in the private gynecology offices and clinics of the Department of Obstetrics, Gynecology and Women's Health at the University of Louisville School of Medicine, under an informed consent protocol approved by the Institutional Review Board at the University. For this proteomics study, eight patients with a history of recurrent spontaneous abortions were enrolled in the study (Table 1). All patients were in good general health and were not taking any medications, except

fractions (FIG. 4). Immunoreactivities for antigens from each cellular compartment were standardized using the pixel values of control standard (HRP-anti-mouse IgG) included in each gel. Duplicate gels were run for each subject and the resulting ratios from the gels were averaged. The mean values and standard deviations were calculated using InStat Graph Pad. Sera from women with a history of RPL exhibited greater immunoreactivities compared to controls, with a total antibody reactivity 1.48-fold greater with nuclear antigens ($p=0.0190$), a 1.57-fold greater reactivity with membrane-derived antigens ($p=0.0056$), and a 1.90-fold greater recognition of cytosolic antigens ($p=0.0162$).

Among IgG subclasses, a notable enhanced recognition pattern was observed in IgG3 with an increase of 1.8-fold greater immunoreactivity compared to controls (FIG. 5). Digitization of the reactive bands demonstrated that this increase was consistently noted across all three antigen sources (nuclear, membrane, and cytosolic antigens), with antigens ranging from 15 to 250 kDa. The enhanced reactivity was linked with the recognition of additional antigenic proteins and not simply greater reactivity with the same components.

Antigen recognition was also determined by immunoprecipitation and protein separation by gel electrophoresis, followed by mass spectrometry, substantially as shown in FIG. 6. In these experiments, Sw.71 cell-line derived nuclear and cellular solubilized proteins (50 µg) were individually sonicated in RIPA buffer (260 µL, containing protease and phosphatase inhibitor cocktails, Sigma Chemical) and incubated with serum-derived immunoglobulins (100 µL) from control (n=2) and test subjects (n=5). The individual samples were then incubated in agarose-bound anti-human IgG (40 µL), centrifuged, and washed to obtain a pellet of immunoprecipitated cellular and nuclear proteins. This was done for each control and test subject. The antigen-antibody complexes were reduced and solubilized using 2× Laemili buffer. Samples were then applied to an 18-well 4-15% Tris-HCL, 1.0 mm, Criterion™ Precast Gel (Bio-Rad, Hercules, Calif.), and separated by electrophoresis. Each gel was then stained using Imperial™ Protein Stain and scanned using PharosFX™ Molecular Imager System (Bio-Rad, Hercules, Calif.).

Specific trophoblast cellular antigens recognized in antibody-antigen binding complexes were defined by mass spectrometry sequencing. The incongruent control and test immunoprecipitation gel spots were removed, washed to remove staining of dye and inhibitory chemicals, and dried to absorb maximum volume of digestion buffer. The dried gel spots were rehydrated in digestion buffer containing sequencing grade modified trypsin (1:30 by mass) and proteins were digested in-gel at 37° C. Digested peptides were extracted from the gel with trifluoroacetic acid extraction buffer and digested tryptic peptides were desalted using C-18 Zip-tips (Millipore). The desalted peptides were mixed with α-cyano-4-hydroxycinnamic acid matrix (CHCA) and spotted into wells of a MALDI plate. Mass spectra (MS) of the peptides in each sample were obtained using Applied Biosystems 4700 Proteomics Analyzer. A minimum of 10 of the most abundant peptides for each sample were further subjected to fragmentation and tandem mass spectrometry (MS/MS) analysis. Protein identification were based on peptide fingerprint mass mapping and peptide fragmentation mapping (using MS/MS spectra). Combined MS and MS/MS spectra were submitted for database search using GPS Explorer software equipped with MASCOT search engine to identify proteins from primary sequence databases.

Specific trophoblast cellular antigens recognized in antibody-antigen binding complexes were defined by immunoprecipitation (FIG. 7) and subsequent mass spectrometry sequencing (Table 2). SDS-PAGE of the immunoprecipitated

proteins derived from membrane and nuclear fractions derived from Sw.71 trophoblast cells revealed numerous qualitative and quantitative differences, as defined by the presence of specific bands (FIG. 7). Subsequent analyses focused on three major bands exhibiting unique association with RPL. Mass spectra (MS) of the peptides in each sample were obtained using Applied Biosystems 4700 Proteomics Analyzer. Protein identification was based on peptide fingerprint mass mapping and peptide fragmentation mapping (using MS/MS spectra). Combined MS+MS/MS analysis was performed using Mascot v 2.1.04 from Matrix Science Ltd and proteins were identified using SwissProt database. Each matched peptide was characterized by an ion score; a high confidence in peptide to protein match was reached when two or more ion scores indicated identity (Table 2). The results include three differently recognized trophoblast antigens: Apolipoprotein B-100 (ApoB-100), fibronectin, and α2-macroglobulin (α2-M). Specifically, recognition of maternal IgG antibodies to trophoblast-derived fibronectin and ApoB-100 were noted when serum was obtained from women who suffer RPL. This antibody recognition was when serum was obtained from pregnant, multiparous women with an uncomplicated obstetrical history. Notably, serum from these same control, multiparous subjects did not revealed antibody recognition to α2M, a pattern that was contrarily absent present in serum from RPL subjects. These findings suggest that perhaps an aberrant maternal antibody recognition of fibronectin and α2M leads to dysfunctional development of the maternal-fetal interface with possible subsequent pregnancy loss or other advanced-gestation obstetrical complications. Concurrently, a combination of the three previously-described functions and mechanisms of action of ApoB may play a vital role in the sustainability of early pregnancy. Perhaps this lack of antibody-ApoB binding, as demonstrated from the serum of healthy controls, alters the intended function of ApoB at the level of the uterine endothelium, the steroid-producing corpus luteal cells, and/or the nutrient-rich embryo yolk sac.

Since paternal genetic material determines at least half the antigenic array of the fetus, expression of these components are capable of eliciting an immune response that can result in the spontaneous loss (abortion) of the fetus. Antibodies that recognize the fetus have been demonstrated in the maternal circulation, and IgG that is reactive with paternal antigens can be eluted from the placenta (Creus et al., *Humm. Reprod.* 13:39-43, 1998; Wilson et al., *Fertil. Steril.* 76:915-917, 2001). In this study, we investigated the antigenic recognition patterns of circulating IgG obtained from women with RPL

TABLE 2

Mass Spectrometry (MS) Protein Identification.					
Serum Source	Protein Identification	Molecular Weight (Da)	Protein Score	Confidence	
				Interval (100%)	Ion Score Notes ¹
Term	α2-Macroglobulin	164614	514	100	7 ion scores indicated identity
			353	100	5 ion scores indicated identity
			239	100	3 ion scores indicated identity
RPL	B100	516666	409	100	5 ion scores indicated identity
RPL	Fibronectin	266034	593	100	7 ion scores indicated identity
			647	100	7 ion scores indicated identity
			652	100	8 ion scores indicated identity
			621	100	7 ion scores indicated identity

TABLE 2-continued

Mass Spectrometry (MS) Protein Identification.					
Serum Source	Protein Identification	Molecular Weight (Da)	Protein Score	Confidence Interval (100%) Ion Score Notes ¹	
			583	100	6 ion scores indicated identity
			694	100	8 ion scores indicated identity

¹Combined MS + MS/MS analysis performed using Mascot v 2.1.04 from Matrix Science Ltd. Proteins were identified using SwissProt database. Protein significance level was 56 by Mascot ($p < 0.05$). The Ion Score Notes refers to matched peptides using Mascot. High confidence in peptide to protein match when two or more ion scores indicate identity.

* = MS also detected serum albumin by 2 ion scores;

+ = MS also detected Ig gamma-2 chain C region & Ig gamma 3 chain C region by 1 ion score. compared with those of pregnant women in the first trimester of uncomplicated pregnancies.

Pregnancy has been shown to produce significant changes within the immune system, generally noted as a shift to a Th2-biased (humoral) immune response. Many of these alterations are not observed in women experiencing RPL. Pregnancy has been associated with the production of Th2 type cytokines (such as IL-10 and IL-4), while RPL has been linked with the production of Th1 type cytokines (such as IFN γ , IL-12). Previous studies have shown that normal uncomplicated pregnancy is associated with significant changes in IgG subclasses (Wilson et al., *Fertil. Steril.* 76:915-917, 2001). Normal pregnancy-associated IL-4 production can induce peripheral blood mononuclear cells to become activated and increase total IgG production, as well as enhanced IgG4. In contrast, RPL-associated IFN- γ production can inhibit these events. RPL is generally associated with reduced levels of IL-10 and these patients exhibit diminished levels of total IgG (Eblen et al., *Fertil. Steril.* 73:305-313, 2000; Wilson et al., *Fertil. Steril.* 76:915-917, 2001).

The present data show that uncomplicated pregnancy is linked with changes in the production of IgG reactive with trophoblast-derived antigens. Pregnant women who subsequently abort exhibited a different IgG subset patterns compared with healthy pregnant women, e.g., increased levels of IgG3. The IgG class of antibody predominates in the blood and interstitial fluids and is the most multi-functional of the all antibody classes. The IgG molecule consists of two antigen binding regions (Fab) and one ligand binding region (Fc) through which various effector activities are initiated (e.g., activation of the classical complement pathway, phagocytosis, and antibody-dependent cellular cytotoxicity) (Jefferis et al., *Ann. Biol. Clin.* 52:57-65, 1994). While generally representing only 7% of total circulating IgG, the IgG3 subclass exhibits the highest complement activation and high affinity for Fc receptors on immune effector cells. Results from this study demonstrate an overall increase in antibody recognition of trophoblastic antigens, as well as distinct antigen-antibody binding patterns (FIGS. 2, 3A-3F, and 4), particularly for IgG3 subclasses (FIG. 5), in women experiencing RPL compared to controls. This increase in IgG3 immunoreactivity, recognized in sera obtained from RPL subjects compared to controls, suggests a higher degree of Th2 immune cell activation and subsequent fetal allograft rejection. Perhaps an atypical ratio of the IgG subclasses in RPL patients, favoring the more immunoreactive IgG3, is a potential link to the mechanism and etiology of recurrent aborters.

In addition to the enhanced recognition of trophoblast-derived antigens by IgG3, patients experiencing RPL, exhibited the recognition of distinct antigenic proteins. Of the trophoblast-derived proteins, we isolated and defined two proteins exhibiting unique antibody recognition in RPL patients: fibronectin and Apolipoprotein B-100, while RPL patients have antibodies that recognize alpha2-macroglobu-

lin. Additional trophoblast-derived antigens recognized in patients experiencing RPL are listed in Table 2.

Alpha2-macroglobulin (α 2M) is homo-tetramer of 180 kDa subunits. It is a major inhibitor of endoproteases and plays a regulatory role in the transport and clearance of cytokines and growth factors. It also may protect against the cytotoxic effects of various cytokines while inhibiting the degradation of other cytokines (Esadeg et al., *Placenta* 24:912-921, 2003). It exists in low serum concentrations in normal healthy adults and, in mammalian blood, it targets cytokines to cells expressing the α 2M-receptor or lipoprotein-receptor related protein (Esadeg et al., *Placenta* 24:912-921, 2003; Shimizu et al., *Exp. Anim.* 51:361-365, 2002). In humans, uterine α 2M is thought to originate from endothelial cells lining the endometrial vessels. Its concentration has been reported to double or triple during the secretory phase of the menstrual cycle suggesting a role as a decidualization protein (Esadeg et al., *Placenta* 24:912-921, 2003). During pregnancy, a receptor for the α 2M-proteinase complex has been demonstrated on the human placental syncytiotrophoblasts (Jensen et al., *Placenta* 9:463-477, 1988; Thomas et al., *Placenta* 11:413-430, 1990). Exhibiting immuno-suppressive activity, α 2M is believed to be a potential means of immunosuppression in the human uteroplacental interface and may be subject to transplacental transport to the neonate (Benyo et al., *Endocrinology* 133:699-704, 1993). In this study, serum obtained from healthy control subjects revealed no antibody recognition to the α 2M tetramer; whereas, serum obtained from pregnant women afflicted with RPL did (FIG. 7, Table 2). With its regulatory role in the activities of leukocytic and non-leukocytic derived cytokines, α 2M may be a key component in the anomalous processes resulting in RPL. The antibody recognition and binding to this protein, as demonstrated from the serum of healthy subjects with RPL, may influence α 2-M activities from various involved sites, including uterine decidualization, endothelial structure, trophoblast invasion and growth, and transplacental transport.

Apolipoprotein B is a core protein of LDL, which mediates the interaction between low density lipoproteins (LDL) and its receptor (Yamada et al., *Hum. Reprod.* 13:944-952, 1998). The principal function of Apolipoprotein B (ApoB-100 and ApoB-48) is to provide a structural framework for packaging neutral lipids, such as triglycerides and cholesterol esters, into lipoproteins for their transportation in an aqueous circulation (Farese et al., *J. Lipid Res.* 37:347-360, 1996). It, furthermore, contains ligands for the receptor-mediated endocytosis of various lipoproteins. Mutations in the LDL-receptor and related proteins have been shown to result in aberrant uptake of ApoB and other lipoproteins into cells. A lack of appropriate lipoprotein control mechanisms ultimately leads to lipoprotein oxidation products that mediate oxidative damage and result in endothelial dysfunction and premature ath-

erosclerosis (Cekmen et al., *Clin. Biochem.* 36:575-578, 2003; Sarandol et al., *Clin. Biochem.* 37:990-996, 2004; Sarandol et al., *Arch. Gynecol. Obstet.* 270:157-160, 2004). In normal pregnancies, there appears to be factors that promote ApoB utilization via receptor mediated endocytosis while protecting it from oxidation and subsequent destructive effects. Trophoblast cells, in particular, express high levels of LDL-receptor and related proteins giving rise to the idea that growth restriction or other vascular obstetrical complications may be associated with a chronic pattern of atherogenic or aberrant lipoprotein metabolism. Perhaps, in normal pregnancy, a specific enzyme or other substrate, protein, or molecule plays a role in stabilizing lipoproteins, inhibiting the common pathway of oxidation. Some researchers have proposed a role for antioxidants such as vitamin E and/or estrogen to inhibit oxidation of lipoproteins (Sarandol et al., *Arch. Gynecol. Obstet.* 270:157-160, 2004). Conversely, the absence of an endogenous protection mechanism may also lead to aberrant lipoprotein oxidative damage at the uteroplacental interface. Such a process may be involved in the circumstances of complicated pregnancies (i.e., RPL, pre-eclampsia, IUGR, etc.).

The expression of ApoB mRNA has been localized in the human embryo yolk endodermal cells by in situ hybridization (Cekmen et al., *Clin. Biochem.* 36:575-578, 2003). While its physiologic purpose in the human yolk sac remains unclear, detection of ApoB in the yolk sac of mice and rats has led to a probable model for transport and packaging of maternally-derived, nutrient rich ApoB-containing lipoproteins into the yolk sac of developing embryo (Cekmen et al., *Clin. Biochem.* 36:575-578, 2003). The humoral recognition of ApoB in affected RPL subjects may play a hostile role in the nutrition of the maturing embryo, hindering normal embryo development.

This study observed maternal IgG antibody recognition of trophoblast-derived ApoB-100 when serum was obtained from pregnant women with history of RPL. This same antibody recognition was not observed when serum was obtained from healthy pregnant controls (FIG. 7). These data suggests that the recognition pattern from test subjects, and lack of recognition by control subjects, may play an aberrant role in lipoprotein metabolism, oxidative destruction, and impairment of endothelial function at the uteroplacental interface. The data show serum antibody recognition of trophoblast-derived ApoB-100 from early pregnancy subjects experiencing RPL. A lack of this recognition was noted when serum was obtained from subjects with a normal obstetrical history. The antibody-ApoB recognition may alter the intended function of ApoB whether at the level of the uterine endothelium, the steroid-producing corpus luteal cells, or the nutrient-rich embryo yolk sac.

Fetal fibronectin is an extracellular matrix protein that is thought of as "trophoblast glue" and is found in increased concentrations at the chorionic-decidual margin and surrounding the extravillous trophoblasts (Guller et al., *Up-to-Date* 17.3, 2009; Mercorio et al., *Eur. J. Obstet. Gynecol. Reprod. Biol.* 126:165-169, 2006). A tightly-regulated balance exists between the activity of the receptive maternal decidua, the invading trophoblast, and developing chorion. Indeed, the maternal extracellular matrix and maternal-fetal interface are thought to play a pivotal role in conditions of

early recurrent abortions, intrauterine growth restriction, and pre-eclampsia. Furthermore, derangement in the autocrine and paracrine signals and receptivity between cellular matrix proteins, such as fibronectin, and cell adhesion molecules may be responsible for pregnancy failure. Acquisition of adhesion-competent invading trophoblast cells is characterized by apical accumulation of integrin receptors for fibronectin and strong fibronectin binding activity on the surface of blastocysts (Mecorio et al., *Eur. J. Obstet. Reprod. Biol.* 126:165-169, 2006). The data herein show the recognition of maternal IgG antibodies to trophoblast-derived fibronectin when serum was obtained from women who suffer a history of RPL (FIG. 7, Table 1). This recognition was absent in healthy, multiparous control subjects. These findings suggest that perhaps aberrant maternal antibody recognition of fibronectin leads to dysfunctional development of the maternal-fetal interface with possible subsequent pregnancy loss or other advanced-gestation obstetrical complications. A growing bulk of evidence suggests an active role of fetal fibronectin in implantation. The autocrine/paracrine control mechanism operating within the decidua has been implicated in the regulation of trophoblast invasion, possibly via modulations of extracellular matrix proteins as fibronectin and its specific integrin trophoblast receptor.

Of particular immunologic importance, fibronectin can regulate production and release of IL-1 β . Due to the profound effects of IL-1 β on immune cell function during inflammation, investigations have focused on the factors that regulate IL-1 β expression. Extracellular matrix components (ECM) can induce the expression of IL-1 β (Roman et al., *Cytokine* 12:1581-1596, 2000). One component well-studied is fibronectin (FN) and this high molecular weight adhesive molecule is expressed by tissue macrophages and fibroblasts. Thus, FN appears to be well positioned to affect the expression of IL-1 β . In vitro studies have demonstrated that FN can stimulate the expression of IL-1 β mRNA, and its translation into the 31 kDa intracellular precursor protein, as well as the secretion of the 17 kDa active form in human mononuclear cells (Roman et al., *Cytokine* 12:1581-1596, 2000). Thus, the production of effector IgG3 reactive with fibronectin may block the FN-induced IL-1 β production. Since IL-1 β serves as a "master" pro-inflammatory regulator associated with early pregnancy, its blockage may prevent the induction of pro-inflammatory environment.

It is likely that these specific trophoblast cellular responses activate various pro-inflammatory or other immunoregulatory activities that inhibit proper implantation and ultimately inhibit growth and survival of the invading trophoblast and developing embryonic cells. This data is clinically useful for screening for women afflicted with RPL and, more importantly, for developing treatment strategies during pre-conceptual and prenatal care.

Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

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<210> SEQ ID NO 2

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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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Glu Asn Val Ser Leu Val Cys Pro Lys Asp Ala Thr Arg Phe Lys His
 35          40          45
Leu Arg Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu Ser Ser Ser Gly Val
 50          55          60
Pro Gly Thr Ala Asp Ser Arg Ser Ala Thr Arg Ile Asn Cys Lys Val
 65          70          75          80
Glu Leu Glu Val Pro Gln Leu Cys Ser Phe Ile Leu Lys Thr Ser Gln
 85          90          95
Cys Thr Leu Lys Glu Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu
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Leu Lys Lys Thr Lys Asn Ser Glu Glu Phe Ala Ala Ala Met Ser Arg
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Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly Lys Gln Val Phe Leu Tyr
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Pro Glu Lys Asp Glu Pro Thr Tyr Ile Leu Asn Ile Lys Arg Gly Ile
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Ile Ser Ala Leu Leu Val Pro Pro Glu Thr Glu Glu Ala Lys Gln Val
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Leu Phe Leu Asp Thr Val Tyr Gly Asn Cys Ser Thr His Phe Thr Val
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Lys Thr Arg Lys Gly Asn Val Ala Thr Glu Ile Ser Thr Glu Arg Asp
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Ala	Ala	Leu	Gly	Lys	Leu	Pro	Gln	Gln	Ala	Asn	Asp	Tyr	Leu	Asn	Ser
					2115						2120			2125	
Phe	Asn	Trp	Glu	Arg	Gln	Val	Ser	His	Ala	Lys	Glu	Lys	Leu	Thr	Ala
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Leu	Thr	Lys	Lys	Tyr	Arg	Ile	Thr	Glu	Asn	Asp	Ile	Gln	Ile	Ala	Leu
					2145						2150			2155	
Asp	Asp	Ala	Lys	Ile	Asn	Phe	Asn	Glu	Lys	Leu	Ser	Gln	Leu	Gln	Thr
					2165						2170			2175	
Tyr	Met	Ile	Gln	Phe	Asp	Gln	Tyr	Ile	Lys	Asp	Ser	Tyr	Asp	Leu	His
					2180						2185			2190	
Asp	Leu	Lys	Ile	Ala	Ile	Ala	Asn	Ile	Ile	Asp	Glu	Ile	Ile	Glu	Lys
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Leu	Lys	Ser	Leu	Asp	Glu	His	Tyr	His	Ile	Arg	Val	Asn	Leu	Val	Lys
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Thr	Ile	His	Asp	Leu	His	Leu	Phe	Ile	Glu	Asn	Ile	Asp	Phe	Asn	Lys
					2225						2230			2235	
Ser	Gly	Ser	Ser	Thr	Ala	Ser	Trp	Ile	Gln	Asn	Val	Asp	Thr	Lys	Tyr
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Gln	Ile	Arg	Ile	Gln	Ile	Gln	Glu	Lys	Leu	Gln	Gln	Leu	Lys	Arg	His
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Ile	Gln	Asn	Ile	Asp	Ile	Gln	His	Leu	Ala	Gly	Lys	Leu	Lys	Gln	His
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Ile	Glu	Ala	Ile	Asp	Val	Arg	Val	Leu	Leu	Asp	Gln	Leu	Gly	Thr	Thr
					2290						2295			2300	
Ile	Ser	Phe	Glu	Arg	Ile	Asn	Asp	Val	Leu	Glu	His	Val	Lys	His	Phe
					2305						2310			2315	
Val	Ile	Asn	Leu	Ile	Gly	Asp	Phe	Glu	Val	Ala	Glu	Lys	Ile	Asn	Ala
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Phe	Arg	Ala	Lys	Val	His	Glu	Leu	Ile	Glu	Arg	Tyr	Glu	Val	Asp	Gln
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Gln	Ile	Gln	Val	Leu	Met	Asp	Lys	Leu	Val	Glu	Leu	Ala	His	Gln	Tyr
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Lys	Leu	Lys	Glu	Thr	Ile	Gln	Lys	Leu	Ser	Asn	Val	Leu	Gln	Gln	Val
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Lys	Ile	Lys	Asp	Tyr	Phe	Glu	Lys	Leu	Val	Gly	Phe	Ile	Asp	Asp	Ala
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Val	Lys	Lys	Leu	Asn	Glu	Leu	Ser	Phe	Lys	Thr	Phe	Ile	Glu	Asp	Val
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Asn	Lys	Phe	Leu	Asp	Met	Leu	Ile	Lys	Lys	Leu	Lys	Ser	Phe	Asp	Tyr
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His	Gln	Phe	Val	Asp	Glu	Thr	Asn	Asp	Lys	Ile	Arg	Glu	Val	Thr	Gln
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 Ala Leu Lys Leu Phe Leu Glu Glu Thr Lys Ala Thr Val Ala Val Tyr
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 Leu Glu Ser Leu Gln Asp Thr Lys Ile Thr Leu Ile Ile Asn Trp Leu
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 Gln Glu Ala Leu Ser Ser Ala Ser Leu Ala His Met Lys Ala Lys Phe
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 Arg Glu Thr Leu Glu Asp Thr Arg Asp Arg Met Tyr Gln Met Asp Ile
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 Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val Gly Gln Val Tyr Ser
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 Thr Leu Val Thr Tyr Ile Ser Asp Trp Trp Thr Leu Ala Ala Lys Asn
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 Ile Leu Gly Thr Met Pro Ala Phe Glu Val Ser Leu Gln Ala Leu Gln
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 Lys Ala Thr Phe Gln Thr Pro Asp Phe Ile Val Pro Leu Thr Asp Leu
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 Ile Pro Ser Arg Phe Ser Thr Pro Glu Phe Thr Ile Leu Asn Thr Phe
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 His Ile Pro Ser Phe Thr Ile Asp Phe Val Glu Met Lys Val Lys Ile
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 Ile Arg Thr Ile Asp Gln Met Leu Asn Ser Glu Leu Gln Trp Pro Val
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 Pro Asp Ile Tyr Leu Arg Asp Leu Lys Val Glu Asp Ile Pro Leu Ala
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 Arg Ile Thr Leu Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile Pro Glu
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 Phe Ile Ile Pro Thr Leu Asn Leu Asn Asp Phe Gln Val Pro Asp Leu
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 His Ile Pro Glu Phe Gln Leu Pro His Ile Ser His Thr Ile Glu Val
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 Pro Thr Phe Gly Lys Leu Tyr Ser Ile Leu Lys Ile Gln Ser Pro Leu
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 Phe Thr Leu Asp Ala Asn Ala Asp Ile Gly Asn Gly Thr Thr Ser Ala
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 Asn Glu Ala Gly Ile Ala Ala Ser Ile Thr Ala Lys Gly Glu Ser Lys
 2785 2790 2795 2800
 Leu Glu Val Leu Asn Phe Asp Phe Gln Ala Asn Ala Gln Leu Ser Asn
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 Pro Lys Ile Asn Pro Leu Ala Leu Lys Glu Ser Val Lys Phe Ser Ser
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 Lys Tyr Leu Arg Thr Glu His Gly Ser Glu Met Leu Phe Phe Gly Asn
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 Ala Ile Glu Gly Lys Ser Asn Thr Val Ala Ser Leu His Thr Glu Lys
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 2980 2985 2990
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 Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu Phe Ile Ser Gln Ser
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 Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn Asn Ala Leu
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 Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile Lys Phe Asp Lys
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 Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro Arg Thr Phe Gln Ile
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 Pro Gly Tyr Thr Val Pro Val Val Asn Val Glu Val Ser Pro Phe Thr
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 Ile Glu Met Ser Ala Phe Gly Tyr Val Phe Pro Lys Ala Val Ser Met
 3265 3270 3275 3280
 Pro Ser Phe Ser Ile Leu Gly Ser Asp Val Arg Val Pro Ser Tyr Thr

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Ile	Phe	Ile	Pro	Ala	Met	Gly	Asn	Ile	Thr	Tyr	Asp	Phe	Ser	Phe	Lys
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Asp	Ile	Val	Ala	His	Leu	Leu	Ser	Ser	Ser	Ser	Ser	Val	Ile	Asp	Ala
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Lys	Gln	Glu	Leu	Asn	Gly	Asn	Thr	Lys	Ser	Lys	Pro	Thr	Val	Ser	Ser
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Gln	Val	His	Ala	Ser	Gln	Pro	Ser	Ser	Phe	His	Asp	Phe	Pro	Asp	Leu
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Asp	Lys	Ser	Leu	Trp	Asp	Phe	Leu	Lys	Leu	Asp	Val	Thr	Thr	Ser	Ile
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Gly	Arg	Arg	Gln	His	Leu	Arg	Val	Ser	Thr	Ala	Phe	Val	Tyr	Thr	Lys
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 Val Met Pro Thr Phe His Val Pro Phe Thr Asp Leu Gln Val Pro Ser
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 Cys Lys Leu Asp Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu Arg Thr
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 Glu Val Asp Val Leu Thr Lys Tyr Ser Gln Pro Glu Asp Ser Leu Ile
 3795 3800 3805
 Pro Phe Phe Glu Ile Thr Val Pro Glu Ser Gln Leu Thr Val Ser Gln
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 Phe Thr Leu Pro Lys Ser Val Ser Asp Gly Ile Ala Ala Leu Asp Leu
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 Leu Tyr Asp Tyr Val Asn Lys Tyr His Trp Glu His Thr Gly Leu Thr
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 Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn Ala
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 Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile Asp Val
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 Lys Asp Lys Ala Gln Asn Leu Tyr Gln Glu Leu Leu Thr Gln Glu Gly
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 Gln Ala Ser Phe Gln Gly Leu Lys Asp Asn Val Phe Asp Gly Leu Val
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 Arg Val Thr Gln Glu Phe His Met Lys Val Lys His Leu Ile Asp Ser
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 Leu Ile Asp Phe Leu Asn Phe Pro Arg Phe Gln Phe Pro Gly Lys Pro
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 Ile Leu Phe Ser Tyr Phe Gln Asp Leu Val Ile Thr Leu Pro Phe Glu
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 Leu Arg Lys His Lys Leu Ile Asp Val Ile Ser Met Tyr Arg Glu Leu
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 Leu Lys Asp Leu Ser Lys Glu Ala Gln Glu Val Phe Lys Ala Ile Gln
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 Ser Leu Lys Thr Thr Glu Val Leu Arg Asn Leu Gln Asp Leu Leu Gln
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 Phe Ser Asp Tyr Ile Pro Tyr Val Phe Lys Leu Leu Lys Glu Asn Leu
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 Cys Leu Asn Leu His Lys Phe Asn Glu Phe Ile Gln Asn Glu Leu Gln
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 Glu Ala Ser Gln Glu Leu Gln Gln Ile His Gln Tyr Ile Met Ala Leu
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 Arg Glu Glu Tyr Phe Asp Pro Ser Ile Val Gly Trp Thr Val Lys Tyr
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 Tyr Glu Leu Glu Glu Lys Ile Val Ser Leu Ile Lys Asn Leu Leu Val
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 Ala Leu Lys Asp Phe His Ser Glu Tyr Ile Val Ser Ala Ser Asn Phe
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 Thr Ser Gln Leu Ser Ser Gln Val Glu Gln Phe Leu His Arg Asn Ile
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 Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp Gly Lys Gly Lys Glu
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 Lys Ile Ala Glu Leu Ser Ala Thr Ala Gln Glu Ile Ile Lys Ser Gln
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 Ala Ile Ala Thr Lys Lys Ile Ile Ser Asp Tyr His Gln Gln Phe Arg
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 Tyr Lys Leu Gln Asp Phe Ser Asp Gln Leu Ser Asp Tyr Tyr Glu Lys
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 Phe Ile Ala Glu Ser Lys Arg Leu Ile Asp Leu Ser Ile Gln Asn Tyr
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 His Thr Phe Leu Ile Tyr Ile Thr Glu Leu Leu Lys Lys Leu Gln Ser
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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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 Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln Ile Gly Asp Ser Trp
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 Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser Ser
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<211> LENGTH: 2402

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

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<210> SEQ ID NO 6

<211> LENGTH: 657

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
 50                55                60

Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
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Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
 85                90                95

Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
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Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly

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 595 600 605
 Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro Asn
 610 615 620
 Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro Ser His Ile Ser Lys
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Tyr

<210> SEQ ID NO 7
 <211> LENGTH: 7912
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

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<210> SEQ ID NO 8

<211> LENGTH: 2176

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser
 35             40             45
Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
 50             55             60
Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
 65             70             75             80

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Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
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 Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
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 Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
 115 120 125
 Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly
 130 135 140
 Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
 145 150 155 160
 Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu
 165 170 175
 Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
 180 185 190
 Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp
 195 200 205
 Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr
 210 215 220
 Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr
 225 230 235 240
 Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu
 245 250 255
 Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg
 260 265 270
 His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp
 275 280 285
 Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro
 290 295 300
 Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met
 305 310 315 320
 Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu
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 Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly
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 Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly
 355 360 365
 Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu
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 Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe
 385 390 395 400
 Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser Asn
 405 410 415
 Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr
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 Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met Lys Trp Cys Gly Thr
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 Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met Ala
 450 455 460
 Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg Ile
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 Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg Cys
 485 490 495
 Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr Ser

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Gln	Leu	Arg	Asp	Gln	Cys	Ile	Val	Asp	Asp	Ile	Thr	Tyr	Asn	Val	Asn
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Asp	Thr	Phe	His	Lys	Arg	His	Glu	Glu	Gly	His	Met	Leu	Asn	Cys	Thr
	530					535					540				
Cys	Phe	Gly	Gln	Gly	Arg	Gly	Arg	Trp	Lys	Cys	Asp	Pro	Val	Asp	Gln
545					550					555					560
Cys	Gln	Asp	Ser	Glu	Thr	Gly	Thr	Phe	Tyr	Gln	Ile	Gly	Asp	Ser	Trp
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Glu	Lys	Tyr	Val	His	Gly	Val	Arg	Tyr	Gln	Cys	Tyr	Cys	Tyr	Gly	Arg
			580					585						590	
Gly	Ile	Gly	Glu	Trp	His	Cys	Gln	Pro	Leu	Gln	Thr	Tyr	Pro	Ser	Ser
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Tyr	Ile	Leu	Arg	Trp	Arg	Pro	Lys	Asn	Ser	Val	Gly	Arg	Trp	Lys	Glu
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Ala	Thr	Ile	Pro	Gly	His	Leu	Asn	Ser	Tyr	Thr	Ile	Lys	Gly	Leu	Lys
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Pro	Gly	Val	Val	Tyr	Glu	Gly	Gln	Leu	Ile	Ser	Ile	Gln	Gln	Tyr	Gly
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His	Gln	Glu	Val	Thr	Arg	Phe	Asp	Phe	Thr	Thr	Thr	Ser	Thr	Ser	Thr
	690					695						700			
Pro	Val	Thr	Ser	Asn	Thr	Val	Thr	Gly	Glu	Thr	Thr	Pro	Phe	Ser	Pro
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Leu	Val	Ala	Thr	Ser	Glu	Ser	Val	Thr	Glu	Ile	Thr	Ala	Ser	Ser	Phe
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Val	Val	Ser	Trp	Val	Ser	Ala	Ser	Asp	Thr	Val	Ser	Gly	Phe	Arg	Val
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Glu	Tyr	Glu	Leu	Ser	Glu	Glu	Gly	Asp	Glu	Pro	Gln	Tyr	Leu	Asp	Leu
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Pro	Ser	Thr	Ala	Thr	Ser	Val	Asn	Ile	Pro	Asp	Leu	Leu	Pro	Gly	Arg
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Lys	Tyr	Ile	Val	Asn	Val	Tyr	Gln	Ile	Ser	Glu	Asp	Gly	Glu	Gln	Ser
785					790					795					800
Leu	Ile	Leu	Ser	Thr	Ser	Gln	Thr	Thr	Ala	Pro	Asp	Ala	Pro	Pro	Asp
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Pro	Thr	Val	Asp	Gln	Val	Asp	Asp	Thr	Ser	Ile	Val	Val	Arg	Trp	Ser
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Arg	Pro	Gln	Ala	Pro	Ile	Thr	Gly	Tyr	Arg	Ile	Val	Tyr	Ser	Pro	Ser
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Val	Glu	Gly	Ser	Ser	Thr	Glu	Leu	Asn	Leu	Pro	Glu	Thr	Ala	Asn	Ser
	850					855						860			
Val	Thr	Leu	Ser	Asp	Leu	Gln	Pro	Gly	Val	Gln	Tyr	Asn	Ile	Thr	Ile
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Tyr	Ala	Val	Glu	Glu	Asn	Gln	Glu	Ser	Thr	Pro	Val	Val	Ile	Gln	Gln
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Glu	Thr	Thr	Gly	Thr	Pro	Arg	Ser	Asp	Thr	Val	Pro	Ser	Pro	Arg	Asp
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Leu	Gln	Phe	Val	Glu	Val	Thr	Asp	Val	Lys	Val	Thr	Ile	Met	Trp	Thr
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Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val
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Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn Thr
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Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys
 965 970 975

Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala Gln
 980 985 990

Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu
 995 1000 1005

Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln Ile
 1010 1015 1020

Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln Pro Arg
 1025 1030 1035 1040

Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr Pro Leu Arg Asn Leu
 1045 1050 1055

Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala Ile Lys Gly Asn
 1060 1065 1070

Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr Thr Leu Gln Pro Gly
 1075 1080 1085

Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr Glu Thr Thr Ile Val
 1090 1095 1100

Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe Lys Leu Gly Val Arg
 1105 1110 1115 1120

Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly
 1125 1130 1135

Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr
 1140 1145 1150

Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp Ala Pro Ile Val Asn
 1155 1160 1165

Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala
 1170 1175 1180

Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr
 1185 1190 1195 1200

Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln
 1205 1210 1215

Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys
 1220 1225 1230

Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr
 1235 1240 1245

Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile Ile
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Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe Thr Asn Ile Gly Pro
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Asp Thr Met Arg Val Thr Trp Ala Pro Pro Pro Ser Ile Asp Leu Thr
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Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn Glu Glu Asp Val Ala
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Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val Val Leu Thr Asn Leu
 1315 1320 1325

Leu Pro Gly Thr Glu Tyr Val Val Ser Val Ser Ser Val Tyr Glu Gln
 1330 1335 1340

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 Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val
 1365 1370 1375
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 His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His
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 1540 1545 1550
 Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu Pro Ser Ser Ser Pro
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 Pro Ser Gly Glu Ser Gln Pro Leu Val Gln Thr Ala Val Thr Thr Ile
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 Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg
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 Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg
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 Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp
 1730 1735 1740
 Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro
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 Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg

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Thr	Gly	Tyr	Ile	Ile	Lys	Tyr	Glu	Lys	Pro	Gly	Ser	Pro	Pro	Arg	Glu
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Val	Val	Pro	Arg	Pro	Arg	Pro	Gly	Val	Thr	Glu	Ala	Thr	Ile	Thr	Gly
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Asn	Gln	Lys	Ser	Glu	Pro	Leu	Ile	Gly	Arg	Lys	Lys	Thr	Gly	Gln	Glu
	1890					1895					1900				
Ala	Leu	Ser	Gln	Thr	Thr	Ile	Ser	Trp	Ala	Pro	Phe	Gln	Asp	Thr	Ser
1905					1910					1915					1920
Glu	Tyr	Ile	Ile	Ser	Cys	His	Pro	Val	Gly	Thr	Asp	Glu	Glu	Pro	Leu
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Gln	Phe	Arg	Val	Pro	Gly	Thr	Ser	Thr	Ser	Ala	Thr	Leu	Thr	Gly	Leu
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Thr	Arg	Gly	Ala	Thr	Tyr	Asn	Ile	Ile	Val	Glu	Ala	Leu	Lys	Asp	Gln
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Gln	Arg	His	Lys	Val	Arg	Glu	Glu	Val	Val	Thr	Val	Gly	Asn	Ser	Val
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Asn	Glu	Gly	Leu	Asn	Gln	Pro	Thr	Asp	Asp	Ser	Cys	Phe	Asp	Pro	Tyr
1985					1990					1995					2000
Thr	Val	Ser	His	Tyr	Ala	Val	Gly	Asp	Glu	Trp	Glu	Arg	Met	Ser	Glu
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Ser	Gly	Phe	Lys	Leu	Leu	Cys	Gln	Cys	Leu	Gly	Phe	Gly	Ser	Gly	His
		2020						2025					2030		
Phe	Arg	Cys	Asp	Ser	Ser	Arg	Trp	Cys	His	Asp	Asn	Gly	Val	Asn	Tyr
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Lys	Ile	Gly	Glu	Lys	Trp	Asp	Arg	Gln	Gly	Glu	Asn	Gly	Gln	Met	Met
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2065					2070					2075					2080
His	Glu	Ala	Thr	Cys	Tyr	Asp	Asp	Gly	Lys	Thr	Tyr	His	Val	Gly	Glu
			2085					2090						2095	
Gln	Trp	Gln	Lys	Glu	Tyr	Leu	Gly	Ala	Ile	Cys	Ser	Cys	Thr	Cys	Phe
		2100						2105					2110		
Gly	Gly	Gln	Arg	Gly	Trp	Arg	Cys	Asp	Asn	Cys	Arg	Arg	Pro	Gly	Gly
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Glu	Pro	Ser	Pro	Glu	Gly	Thr	Thr	Gly	Gln	Ser	Tyr	Asn	Gln	Tyr	Ser
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Gln	Arg	Tyr	His	Gln	Arg	Thr	Asn	Thr	Asn	Val	Asn	Cys	Pro	Ile	Glu
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Cys	Phe	Met	Pro	Leu	Asp	Val	Gln	Ala	Asp	Arg	Glu	Asp	Ser	Arg	Glu
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<211> LENGTH: 8647

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser
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Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
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 Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
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 Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
 100 105 110
 Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
 115 120 125
 Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly
 130 135 140
 Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
 145 150 155 160
 Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu
 165 170 175
 Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
 180 185 190
 Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp
 195 200 205
 Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr
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 Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr
 225 230 235 240
 Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu
 245 250 255
 Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg
 260 265 270
 His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp
 275 280 285
 Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro
 290 295 300
 Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met
 305 310 315 320
 Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu
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 Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly
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 Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly
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 Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu
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 Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe
 385 390 395 400
 Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser Asn
 405 410 415
 Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr
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 Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met Lys Trp Cys Gly Thr
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 Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met Ala
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 Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg Ile
 465 470 475 480
 Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg Cys

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Cys	Phe	Gly	Gln	Gly	Arg	Gly	Arg	Trp	Lys	Cys	Asp	Pro	Val	Asp	Gln
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Cys	Gln	Asp	Ser	Glu	Thr	Gly	Thr	Phe	Tyr	Gln	Ile	Gly	Asp	Ser	Trp
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Glu	Lys	Tyr	Val	His	Gly	Val	Arg	Tyr	Gln	Cys	Tyr	Cys	Tyr	Gly	Arg
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Gly	Ile	Gly	Glu	Trp	His	Cys	Gln	Pro	Leu	Gln	Thr	Tyr	Pro	Ser	Ser
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Ser	Gly	Pro	Val	Glu	Val	Phe	Ile	Thr	Glu	Thr	Pro	Ser	Gln	Pro	Asn
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Ser	His	Pro	Ile	Gln	Trp	Asn	Ala	Pro	Gln	Pro	Ser	His	Ile	Ser	Lys
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Tyr	Ile	Leu	Arg	Trp	Arg	Pro	Lys	Asn	Ser	Val	Gly	Arg	Trp	Lys	Glu
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Ala	Thr	Ile	Pro	Gly	His	Leu	Asn	Ser	Tyr	Thr	Ile	Lys	Gly	Leu	Lys
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His	Gln	Glu	Val	Thr	Arg	Phe	Asp	Phe	Thr	Thr	Thr	Ser	Thr	Ser	Thr
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Pro	Val	Thr	Ser	Asn	Thr	Val	Thr	Gly	Glu	Thr	Thr	Pro	Phe	Ser	Pro
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Leu	Val	Ala	Thr	Ser	Glu	Ser	Val	Thr	Glu	Ile	Thr	Ala	Ser	Ser	Phe
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Val	Val	Ser	Trp	Val	Ser	Ala	Ser	Asp	Thr	Val	Ser	Gly	Phe	Arg	Val
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		755					760						765		
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Lys	Tyr	Ile	Val	Asn	Val	Tyr	Gln	Ile	Ser	Glu	Asp	Gly	Glu	Gln	Ser
785						790							795		800
Leu	Ile	Leu	Ser	Thr	Ser	Gln	Thr	Thr	Ala	Pro	Asp	Ala	Pro	Pro	Asp
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Pro	Thr	Val	Asp	Gln	Val	Asp	Asp	Thr	Ser	Ile	Val	Val	Arg	Trp	Ser
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Arg	Pro	Gln	Ala	Pro	Ile	Thr	Gly	Tyr	Arg	Ile	Val	Tyr	Ser	Pro	Ser
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Val	Glu	Gly	Ser	Ser	Thr	Glu	Leu	Asn	Leu	Pro	Glu	Thr	Ala	Asn	Ser
	850						855						860		
Val	Thr	Leu	Ser	Asp	Leu	Gln	Pro	Gly	Val	Gln	Tyr	Asn	Ile	Thr	Ile
865							870						875		880
Tyr	Ala	Val	Glu	Glu	Asn	Gln	Glu	Ser	Thr	Pro	Val	Val	Ile	Gln	Gln
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Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val
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Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys
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Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala Gln
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Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu
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Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln Ile
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Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln Pro Arg
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Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala Ile Lys Gly Asn
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Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr Thr Leu Gln Pro Gly
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Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr Glu Thr Thr Ile Val
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Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe Lys Leu Gly Val Arg
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Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly
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Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr
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Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala
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Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln
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Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys
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Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr
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Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile Ile
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Pro Glu Val Pro Gln Leu Thr Asp Leu Ser Phe Val Asp Ile Thr Asp
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Ser Ser Ile Gly Leu Arg Trp Thr Pro Leu Asn Ser Ser Thr Ile Ile
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Gly Glu Ser Ala Pro Thr Thr Leu Thr Gln Gln Thr Ala Val Pro Pro
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Thr Trp Ala Pro Pro Pro Ser Ile Asp Leu Thr Asn Phe Leu Val Arg
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Tyr Ser Pro Val Lys Asn Glu Glu Asp Val Ala Glu Leu Ser Ile Ser
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Pro Ser Asp Asn Ala Val Val Leu Thr Asn Leu Leu Pro Gly Thr Glu
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Tyr Val Val Ser Val Ser Ser Val Tyr Glu Gln His Glu Ser Thr Pro
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Leu Arg Gly Arg Gln Lys Thr Gly Leu Asp Ser Pro Thr Gly Ile Asp
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Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val His Trp Ile Ala Pro
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Arg Ala Thr Ile Thr Gly Tyr Arg Ile Arg His His Pro Glu His Phe
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Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His Ser Arg Asn Ser Ile
 1490 1495 1500

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Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu Ile Gly Gln Gln Ser
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Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr
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Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu
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Phe Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys
 1585 1590 1595 1600

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Gly Arg Gly
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Ile Ser Val Lys Trp Leu Pro Ser Ser Ser Pro Val Thr Gly Tyr Arg
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Val Thr Thr Thr Pro Lys Asn Gly Pro Gly Pro Thr Lys Thr Lys Thr
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Ala Gly Pro Asp Gln Thr Glu Met Thr Ile Glu Gly Leu Gln Pro Thr
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Val Glu Tyr Val Val Ser Val Tyr Ala Gln Asn Pro Ser Gly Glu Ser
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Gln Pro Leu Val Gln Thr Ala Val Thr Asn Ile Asp Arg Pro Lys Gly
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Leu Ala Phe Thr Asp Val Asp Val Asp Ser Ile Lys Ile Ala Trp Glu
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Ser Pro Gln Gly Gln Val Ser Arg Tyr Arg Val Thr Tyr Ser Ser Pro

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Val Val Ala Leu His Asp Asp Met Glu Ser Gln Pro Leu Ile Gly Thr	1795	1800	1805
Gln Ser Thr Ala Ile Pro Ala Pro Thr Asp Leu Lys Phe Thr Gln Val	1810	1815	1820
Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro Pro Asn Val Gln Leu	1825	1830	1835
Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu Lys Thr Gly Pro Met	1845	1850	1855
Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly	1860	1865	1870
Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp	1875	1880	1885
Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn	1890	1895	1900
Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr	1905	1910	1915
Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln	1925	1930	1935
Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile	1940	1945	1950
Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr	1955	1960	1965
Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser	1970	1975	1980
Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu	1985	1990	1995
Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln Pro	2005	2010	2015
Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly	2020	2025	2030
Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro Gly Val Thr Glu	2035	2040	2045
Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val	2050	2055	2060
Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys	2065	2070	2075
Lys Thr Val Gln Lys Thr Pro Phe Val Thr His Pro Gly Tyr Asp Thr	2085	2090	2095
Gly Asn Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln Pro Ser Val	2100	2105	2110
Gly Gln Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg Thr Thr Pro	2115	2120	2125
Pro Thr Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro Tyr Pro Pro	2130	2135	2140
Asn Val Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser Trp Ala Pro	2145	2150	2155
Phe Gln Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro Val Gly Thr	2165	2170	2175

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 Cys Phe Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly Asp Glu Trp
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 Glu Arg Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly
 2260 2265 2270
 Phe Gly Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp
 2275 2280 2285
 Asn Gly Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu
 2290 2295 2300
 Asn Gly Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu
 2305 2310 2315 2320
 Phe Lys Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr
 2325 2330 2335
 Tyr His Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys
 2340 2345 2350
 Ser Cys Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys
 2355 2360 2365
 Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser
 2370 2375 2380
 Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val
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<210> SEQ ID NO 12

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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser
          35          40          45
Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
          50          55          60
Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
          65          70          75          80
Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
          85          90          95
Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
          100          105          110
Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
          115          120          125
Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly
          130          135          140
Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
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Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu
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Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
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Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp
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Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr
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Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr
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Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg
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His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp
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Gly	Leu	Gln	Pro	Thr	Val	Glu	Tyr	Val	Val	Ser	Val	Tyr	Ala	Gln	Asn	1605	1610	1615
Pro	Ser	Gly	Glu	Ser	Gln	Pro	Leu	Val	Gln	Thr	Ala	Val	Thr	Thr	Ile	1620	1625	1630
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Gln	Pro	Ser	Val	Gly	Gln	Gln	Met	Ile	Phe	Glu	Glu	His	Gly	Phe	Arg	1955	1960	1965
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Cys Leu Gly Phe Gly Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp 2145 2150 2155 2160		
Cys His Asp Asn Gly Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg 2165 2170 2175		
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Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr 2245 2250 2255		
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 <213> ORGANISM: Homo sapiens

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<212> TYPE: PRT

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<210> SEQ ID NO 16

<211> LENGTH: 2477

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

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 35 40 45
 Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
 50 55 60
 Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
 65 70 75 80
 Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
 85 90 95
 Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
 100 105 110
 Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
 115 120 125
 Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly
 130 135 140
 Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
 145 150 155 160
 Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu
 165 170 175
 Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
 180 185 190
 Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp
 195 200 205
 Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr
 210 215 220
 Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr
 225 230 235 240
 Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu
 245 250 255
 Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg
 260 265 270
 His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp
 275 280 285
 Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro
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 Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met
 305 310 315 320
 Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu
 325 330 335
 Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly
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 Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly
 355 360 365
 Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu
 370 375 380
 Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe
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 Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser Asn
 405 410 415
 Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr

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Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn Ser
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 Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr Ile
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 Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln Gln
 885 890 895
 Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg Asp
 900 905 910
 Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp Thr
 915 920 925
 Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val
 930 935 940
 Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn Thr
 945 950 955 960
 Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys
 965 970 975
 Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala Gln
 980 985 990
 Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu
 995 1000 1005
 Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln Ile
 1010 1015 1020
 Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln Pro Arg
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 Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr Pro Leu Arg Asn Leu
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 Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala Ile Lys Gly Asn
 1060 1065 1070
 Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr Thr Leu Gln Pro Gly
 1075 1080 1085
 Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr Glu Thr Thr Ile Val
 1090 1095 1100
 Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe Lys Leu Gly Val Arg
 1105 1110 1115 1120
 Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly
 1125 1130 1135
 Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr
 1140 1145 1150
 Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp Ala Pro Ile Val Asn
 1155 1160 1165
 Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala
 1170 1175 1180
 Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr
 1185 1190 1195 1200
 Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln
 1205 1210 1215
 Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys
 1220 1225 1230
 Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr
 1235 1240 1245
 Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile Ile
 1250 1255 1260

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Pro Glu Val Pro Gln Leu Thr Asp Leu Ser Phe Val Asp Ile Thr Asp
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 Ser Ser Ile Gly Leu Arg Trp Thr Pro Leu Asn Ser Ser Thr Ile Ile
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 Gly Tyr Arg Ile Thr Val Val Ala Ala Gly Glu Gly Ile Pro Ile Phe
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 Glu Asp Phe Val Asp Ser Ser Val Gly Tyr Tyr Thr Val Thr Gly Leu
 1315 1320 1325
 Glu Pro Gly Ile Asp Tyr Asp Ile Ser Val Ile Thr Leu Ile Asn Gly
 1330 1335 1340
 Gly Glu Ser Ala Pro Thr Thr Leu Thr Gln Gln Thr Ala Val Pro Pro
 1345 1350 1355 1360
 Pro Thr Asp Leu Arg Phe Thr Asn Ile Gly Pro Asp Thr Met Arg Val
 1365 1370 1375
 Thr Trp Ala Pro Pro Pro Ser Ile Asp Leu Thr Asn Phe Leu Val Arg
 1380 1385 1390
 Tyr Ser Pro Val Lys Asn Glu Glu Asp Val Ala Glu Leu Ser Ile Ser
 1395 1400 1405
 Pro Ser Asp Asn Ala Val Val Leu Thr Asn Leu Leu Pro Gly Thr Glu
 1410 1415 1420
 Tyr Val Val Ser Val Ser Ser Val Tyr Glu Gln His Glu Ser Thr Pro
 1425 1430 1435 1440
 Leu Arg Gly Arg Gln Lys Thr Gly Leu Asp Ser Pro Thr Gly Ile Asp
 1445 1450 1455
 Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val His Trp Ile Ala Pro
 1460 1465 1470
 Arg Ala Thr Ile Thr Gly Tyr Arg Ile Arg His His Pro Glu His Phe
 1475 1480 1485
 Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His Ser Arg Asn Ser Ile
 1490 1495 1500
 Thr Leu Thr Asn Leu Thr Pro Gly Thr Glu Tyr Val Val Ser Ile Val
 1505 1510 1515 1520
 Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu Ile Gly Gln Gln Ser
 1525 1530 1535
 Thr Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro
 1540 1545 1550
 Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr
 1555 1560 1565
 Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu
 1570 1575 1580
 Phe Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys
 1585 1590 1595 1600
 Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Gly Arg Gly
 1605 1610 1615
 Asp Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr Glu
 1620 1625 1630
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 1635 1640 1645
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 Val Thr Thr Thr Pro Lys Asn Gly Pro Gly Pro Thr Lys Thr Lys Thr
 1665 1670 1675 1680
 Ala Gly Pro Asp Gln Thr Glu Met Thr Ile Glu Gly Leu Gln Pro Thr

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Gln	Pro	Leu	Val	Gln	Thr	Ala	Val	Thr	Asn	Ile	Asp	Arg	Pro	Lys	Gly
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Leu	Ala	Phe	Thr	Asp	Val	Asp	Val	Asp	Ser	Ile	Lys	Ile	Ala	Trp	Glu
		1730				1735					1740				
Ser	Pro	Gln	Gly	Gln	Val	Ser	Arg	Tyr	Arg	Val	Thr	Tyr	Ser	Ser	Pro
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Glu	Asp	Gly	Ile	His	Glu	Leu	Phe	Pro	Ala	Pro	Asp	Gly	Glu	Glu	Asp
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Thr	Ala	Glu	Leu	Gln	Gly	Leu	Arg	Pro	Gly	Ser	Glu	Tyr	Thr	Val	Ser
			1780							1785				1790	
Val	Val	Ala	Leu	His	Asp	Asp	Met	Glu	Ser	Gln	Pro	Leu	Ile	Gly	Thr
			1795							1800				1805	
Gln	Ser	Thr	Ala	Ile	Pro	Ala	Pro	Thr	Asp	Leu	Lys	Phe	Thr	Gln	Val
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Thr	Pro	Thr	Ser	Leu	Ser	Ala	Gln	Trp	Thr	Pro	Pro	Asn	Val	Gln	Leu
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Thr	Gly	Tyr	Arg	Val	Arg	Val	Thr	Pro	Lys	Glu	Lys	Thr	Gly	Pro	Met
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Lys	Glu	Ile	Asn	Leu	Ala	Pro	Asp	Ser	Ser	Ser	Val	Val	Val	Ser	Gly
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Leu	Met	Val	Ala	Thr	Lys	Tyr	Glu	Val	Ser	Val	Tyr	Ala	Leu	Lys	Asp
			1875				1880							1885	
Thr	Leu	Thr	Ser	Arg	Pro	Ala	Gln	Gly	Val	Val	Thr	Thr	Leu	Glu	Asn
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Val	Ser	Pro	Pro	Arg	Arg	Ala	Arg	Val	Thr	Asp	Ala	Thr	Glu	Thr	Thr
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Ile	Thr	Ile	Ser	Trp	Arg	Thr	Lys	Thr	Glu	Thr	Ile	Thr	Gly	Phe	Gln
			1925							1930				1935	
Val	Asp	Ala	Val	Pro	Ala	Asn	Gly	Gln	Thr	Pro	Ile	Gln	Arg	Thr	Ile
			1940							1945				1950	
Lys	Pro	Asp	Val	Arg	Ser	Tyr	Thr	Ile	Thr	Gly	Leu	Gln	Pro	Gly	Thr
			1955				1960							1965	
Asp	Tyr	Lys	Ile	Tyr	Leu	Tyr	Thr	Leu	Asn	Asp	Asn	Ala	Arg	Ser	Ser
			1970				1975							1980	
Pro	Val	Val	Ile	Asp	Ala	Ser	Thr	Ala	Ile	Asp	Ala	Pro	Ser	Asn	Leu
			1985			1990				1995				2000	
Arg	Phe	Leu	Ala	Thr	Thr	Pro	Asn	Ser	Leu	Leu	Val	Ser	Trp	Gln	Pro
			2005							2010				2015	
Pro	Arg	Ala	Arg	Ile	Thr	Gly	Tyr	Ile	Ile	Lys	Tyr	Glu	Lys	Pro	Gly
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Ser	Pro	Pro	Arg	Glu	Val	Val	Pro	Arg	Pro	Arg	Pro	Gly	Val	Thr	Glu
			2035				2040							2045	
Ala	Thr	Ile	Thr	Gly	Leu	Glu	Pro	Gly	Thr	Glu	Tyr	Thr	Ile	Tyr	Val
			2050			2055								2060	
Ile	Ala	Leu	Lys	Asn	Asn	Gln	Lys	Ser	Glu	Pro	Leu	Ile	Gly	Arg	Lys
			2065			2070				2075				2080	
Lys	Thr	Asp	Glu	Leu	Pro	Gln	Leu	Val	Thr	Leu	Pro	His	Pro	Asn	Leu
			2085							2090				2095	
His	Gly	Pro	Glu	Ile	Leu	Asp	Val	Pro	Ser	Thr	Val	Gln	Lys	Thr	Pro
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<210> SEQ ID NO 18

<211> LENGTH: 1474

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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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 20              25              30
Val Leu Val Pro Ser Leu Leu His Thr Glu Thr Thr Glu Lys Gly Cys
 35              40              45
Val Leu Leu Ser Tyr Leu Asn Glu Thr Val Thr Val Ser Ala Ser Leu
 50              55              60
Glu Ser Val Arg Gly Asn Arg Ser Leu Phe Thr Asp Leu Glu Ala Glu
 65              70              75              80
Asn Asp Val Leu His Cys Val Ala Phe Ala Val Pro Lys Ser Ser Ser
 85              90              95
Asn Glu Glu Val Met Phe Leu Thr Val Gln Val Lys Gly Pro Thr Gln
 100             105             110
Glu Phe Lys Lys Arg Thr Thr Val Met Val Lys Asn Glu Asp Ser Leu
 115             120             125
Val Phe Val Gln Thr Asp Lys Ser Ile Tyr Lys Pro Gly Gln Thr Val
 130             135             140
Lys Phe Arg Val Val Ser Met Asp Glu Asn Phe His Pro Leu Asn Glu
 145             150             155             160
Leu Ile Pro Leu Val Tyr Ile Gln Asp Pro Lys Gly Asn Arg Ile Ala
 165             170             175
Gln Trp Gln Ser Phe Gln Leu Glu Gly Gly Leu Lys Gln Phe Ser Phe
 180             185             190
Pro Leu Ser Ser Glu Pro Phe Gln Gly Ser Tyr Lys Val Val Val Gln
 195             200             205
Lys Lys Ser Gly Gly Arg Thr Glu His Pro Phe Thr Val Glu Glu Phe
 210             215             220
Val Leu Pro Lys Phe Glu Val Gln Val Thr Val Pro Lys Ile Ile Thr
 225             230             235             240
Ile Leu Glu Glu Glu Met Asn Val Ser Val Cys Gly Leu Tyr Thr Tyr
 245             250             255
Gly Lys Pro Val Pro Gly His Val Thr Val Ser Ile Cys Arg Lys Tyr
 260             265             270
Ser Asp Ala Ser Asp Cys His Gly Glu Asp Ser Gln Ala Phe Cys Glu
 275             280             285
Lys Phe Ser Gly Gln Leu Asn Ser His Gly Cys Phe Tyr Gln Gln Val
 290             295             300
Lys Thr Lys Val Phe Gln Leu Lys Arg Lys Glu Tyr Glu Met Lys Leu
 305             310             315             320
His Thr Glu Ala Gln Ile Gln Glu Glu Gly Thr Val Val Glu Leu Thr
 325             330             335
Gly Arg Gln Ser Ser Glu Ile Thr Arg Thr Ile Thr Lys Leu Ser Phe
 340             345             350
Val Lys Val Asp Ser His Phe Arg Gln Gly Ile Pro Phe Phe Gly Gln
 355             360             365
Val Arg Leu Val Asp Gly Lys Gly Val Pro Ile Pro Asn Lys Val Ile
 370             375             380
Phe Ile Arg Gly Asn Glu Ala Asn Tyr Tyr Ser Asn Ala Thr Thr Asp
 385             390             395             400

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Tyr Leu Pro Lys Cys Ile Arg Val Ser Val Gln Leu Glu Ala Ser Pro
 820 825 830

Ala Phe Leu Ala Val Pro Val Glu Lys Glu Gln Ala Pro His Cys Ile
 835 840 845

Cys Ala Asn Gly Arg Gln Thr Val Ser Trp Ala Val Thr Pro Lys Ser
 850 855 860

Leu Gly Asn Val Asn Phe Thr Val Ser Ala Glu Ala Leu Glu Ser Gln
 865 870 875 880

Glu Leu Cys Gly Thr Glu Val Pro Ser Val Pro Glu His Gly Arg Lys
 885 890 895

Asp Thr Val Ile Lys Pro Leu Leu Val Glu Pro Glu Gly Leu Glu Lys
 900 905 910

Glu Thr Thr Phe Asn Ser Leu Leu Cys Pro Ser Gly Gly Glu Val Ser
 915 920 925

Glu Glu Leu Ser Leu Lys Leu Pro Pro Asn Val Val Glu Glu Ser Ala
 930 935 940

Arg Ala Ser Val Ser Val Leu Gly Asp Ile Leu Gly Ser Ala Met Gln
 945 950 955 960

Asn Thr Gln Asn Leu Leu Gln Met Pro Tyr Gly Cys Gly Glu Gln Asn
 965 970 975

Met Val Leu Phe Ala Pro Asn Ile Tyr Val Leu Asp Tyr Leu Asn Glu
 980 985 990

Thr Gln Gln Leu Thr Pro Glu Ile Lys Ser Lys Ala Ile Gly Tyr Leu
 995 1000 1005

Asn Thr Gly Tyr Gln Arg Gln Leu Asn Tyr Lys His Tyr Asp Gly Ser
 1010 1015 1020

Tyr Ser Thr Phe Gly Glu Arg Tyr Gly Arg Asn Gln Gly Asn Thr Trp
 1025 1030 1035 1040

Leu Thr Ala Phe Val Leu Lys Thr Phe Ala Gln Ala Arg Ala Tyr Ile
 1045 1050 1055

Phe Ile Asp Glu Ala His Ile Thr Gln Ala Leu Ile Trp Leu Ser Gln
 1060 1065 1070

Arg Gln Lys Asp Asn Gly Cys Phe Arg Ser Ser Gly Ser Leu Leu Asn
 1075 1080 1085

Asn Ala Ile Lys Gly Gly Val Glu Asp Glu Val Thr Leu Ser Ala Tyr
 1090 1095 1100

Ile Thr Ile Ala Leu Leu Glu Ile Pro Leu Thr Val Thr His Pro Val
 1105 1110 1115 1120

Val Arg Asn Ala Leu Phe Cys Leu Glu Ser Ala Trp Lys Thr Ala Gln
 1125 1130 1135

Glu Gly Asp His Gly Ser His Val Tyr Thr Lys Ala Leu Leu Ala Tyr
 1140 1145 1150

Ala Phe Ala Leu Ala Gly Asn Gln Asp Lys Arg Lys Glu Val Leu Lys
 1155 1160 1165

Ser Leu Asn Glu Glu Ala Val Lys Lys Asp Asn Ser Val His Trp Glu
 1170 1175 1180

Arg Pro Gln Lys Pro Lys Ala Pro Val Gly His Phe Tyr Glu Pro Gln
 1185 1190 1195 1200

Ala Pro Ser Ala Glu Val Glu Met Thr Ser Tyr Val Leu Leu Ala Tyr
 1205 1210 1215

Leu Thr Ala Gln Pro Ala Pro Thr Ser Glu Asp Leu Thr Ser Ala Thr
 1220 1225 1230

Asn Ile Val Lys Trp Ile Thr Lys Gln Gln Asn Ala Gln Gly Gly Phe

-continued

1235	1240	1245
Ser Ser Thr Gln Asp Thr Val Val Ala Leu His Ala Leu Ser Lys Tyr 1250 1255 1260		
Gly Ala Ala Thr Phe Thr Arg Thr Gly Lys Ala Ala Gln Val Thr Ile 1265 1270 1275 1280		
Gln Ser Ser Gly Thr Phe Ser Ser Lys Phe Gln Val Asp Asn Asn Asn 1285 1290 1295		
Arg Leu Leu Leu Gln Gln Val Ser Leu Pro Glu Leu Pro Gly Glu Tyr 1300 1305 1310		
Ser Met Lys Val Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu 1315 1320 1325		
Lys Tyr Asn Ile Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly 1330 1335 1340		
Val Gln Thr Leu Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser 1345 1350 1355 1360		
Phe Gln Ile Ser Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser 1365 1370 1375		
Asn Met Ala Ile Val Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu 1380 1385 1390		
Lys Pro Thr Val Lys Met Leu Glu Arg Ser Asn His Val Ser Arg Thr 1395 1400 1405		
Glu Val Ser Ser Asn His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn 1410 1415 1420		
Gln Thr Leu Ser Leu Phe Phe Thr Val Leu Gln Asp Val Pro Val Arg 1425 1430 1435 1440		
Asp Leu Lys Pro Ala Ile Val Lys Val Tyr Asp Tyr Tyr Glu Thr Asp 1445 1450 1455		
Glu Phe Ala Ile Ala Glu Tyr Asn Ala Pro Cys Ser Lys Asp Leu Gly 1460 1465 1470		
Asn Ala		

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What is claimed is:

1. A method for predicting risk of pregnancy loss in a subject, the method comprising:

- (a) providing a sample comprising serum from the subject; and
- (b) performing an assay to detect the presence of antibodies to fibronectin and antibodies to alpha2-macroglobulin (α 2M) in the sample;
- (c) identifying the subject as having an increased risk of pregnancy loss based on the presence of antibodies to fibronectin and α 2M in the sample.

2. The method of any claim 1, wherein detecting the presence or absence of antibodies comprises contacting the sample with one fibronectin and α 2M, or antigenic fragments thereof, and detecting binding of antibodies in the sample to the fibronectin and α 2M.

3. A method of selecting a subject for participation in a clinical study of recurrent pregnancy loss comprising:

- (a) providing a sample comprising serum from the subject; and
- (b) detecting the presence or absence of antibodies to fibronectin and α 2M in the sample, and
- (c) selecting a subject having antibodies to fibronectin and α 2M present in the sample of (a) is selected for participation in said clinical study.

4. The method of claim 3, wherein detecting the presence or absence of antibodies comprises contacting the sample

with fibronectin and α 2M, or antigenic fragments thereof, and detecting binding of antibodies in the sample to the fibronectin and α 2M.

5. A method of decreasing the risk of pregnancy loss in a subject comprising:

- (a) providing a sample comprising serum from the subject;
- (b) detecting the presence of antibodies to fibronectin and α 2M in the sample; and
- (c) administering a therapeutic treatment to a subject having antibodies to fibronectin and α 2M present in the sample of (a).

6. The method of claim 1, wherein the subject has had at least one previous pregnancy loss or is suspected of having had at least one previous pregnancy loss.

7. The method of claim 1, wherein the subject is not pregnant, but is planning or considering a future pregnancy.

8. The method of claim 1, wherein the subject is pregnant.

9. The method of claim 1, wherein the sample in (a) is obtained from the subject within the first 20 weeks, within the first 13 weeks, or within the first 12 weeks of pregnancy.

10. The method of claim 5, wherein detecting the presence of antibodies comprises contacting the sample with fibronectin and α 2M, or antigenic fragments thereof, and detecting binding of antibodies in the sample to the fibronectin and α 2M.

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11. The method of claim 1, wherein the subject is human.

12. The method of claim 5, wherein said therapeutic treatment is selected from the group consisting of: complement inhibitors, hormone treatment, steroid treatment, passive immunotherapy with intravenous immunoglobulins, aspirin, 5 and tumor necrosis factor (TNF)- α antagonists.

13. The method of claim 5, wherein the subject has had at least one previous pregnancy loss or is suspected of having had at least one previous pregnancy loss.

14. The method of claim 5, wherein the subject is not 10 pregnant, but is planning or considering a future pregnancy.

15. The method of claim 5, wherein the subject is pregnant.

16. The method of claim 5, wherein the sample in (a) is obtained from the subject within the first 20 weeks, within the first 13 weeks, or within the first 12 weeks of pregnancy. 15

17. The method of claim 5, wherein the subject is human.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,068,990 B2
APPLICATION NO. : 14/276601
DATED : June 30, 2015
INVENTOR(S) : Douglas D. Taylor, Cicek Gerchel-Taylor and Rhiana Dawn Saunders

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page

Item (72) Inventors, line 6, delete "Louisville, KY" and insert -- Monmouth Junction --;

Item (72) Inventors, line 7, delete "Louisville, KY" and insert -- Monmouth Junction --;

Item (72) Inventors, after line 7, insert -- Rhiana Dawn Saunders, San Antonio, TX (US) --;

In the claims

In column 197, line 52, in Claim 2, delete "of any" and insert -- of --;

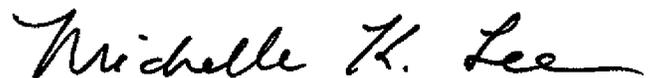
In column 197, line 53, in Claim 2, delete "presence or absence" and insert -- presence --;

In column 197, line 54, in Claim 2, delete "with one" and insert -- with --;

In column 197, line 64, in Claim 3, delete "(a) is selected" and insert -- (a) --;

In column 197, line 67, in Claim 4, delete "presence or absence" and insert -- presence --.

Signed and Sealed this
Second Day of February, 2016



Michelle K. Lee
Director of the United States Patent and Trademark Office